



Systematic study on acylation of methyl 3-aminocrotonate with acid chlorides of aliphatic, aromatic and α , β -unsaturated acids: A comparative evaluation of the preference for regio- and stereoselectivity *vis-à-vis* 3-aminocrotonitrile

Attreyee Mukherjee^a & Kumar K Mahalanabis*^b

^a Ananda Mohan College, Kolkata 700 009, India

^b Jadavpur University, Kolkata 700 032, India

E-mail: kkmahalanabis@gmail.com; attreyee.m@gmail.com

Received 6 December 2019; accepted (revised) 11 January 2021

Acylation of methyl 3-aminocrotonate **1a** in benzene with a variety of aliphatic and aromatic acid chlorides including α , β -unsaturated acid chloride in the presence of an added organic base, (either pyridine or triethylamine) is reported. The preferred N, C-site selectivity in these reactions has been compared with the terminal selectivity of the products obtained previously on acylation of methyl 3-aminocrotonitrile **1b**. A strong preference either for N- or C- selectivity in N, C-acylation has been observed for both **1a** and **1b** based on the choice of acid chlorides and added organic base. Interestingly, irrespective of the enamine **1a** or **1b**, acylation with α , β -unsaturated acid chlorides in the presence of triethylamine afforded 3,4-dihydropyridin-(2*H*)-one *via* [3.3] sigmatropic rearrangement of the corresponding intermediary N(E)-enamide. Accrued results show methyl 3-aminocrotonate to be a better precursor for preparation of enamides (N-acylated products) whereas 3-aminocrotonitrile is found to be a preferred choice for preparation of enamines (C-acylated products). An attempt is made to offer a preliminary theoretical interpretation for observed site selectivity.

Keywords: Methyl 3-aminocrotonate, acylation, enamines, enamides, regioselective, stereoselective

Enamines represent a three atom π -system, and in principle, can react with an electrophile either on nitrogen or on carbon leading to the formation of enamides (N-acylated) or enamines¹ (C-acylated). Chemistry of enamines are reported extensively but these are mostly related to tertiary cyclic enamines. In sharp contrast, significantly much less work were reported on the chemistry of acyclic primary enamines and enaminoesters². Enaminoesters are versatile, readily available highly important synthetic intermediates and building blocks in organic chemistry³ particularly in the synthesis of heterocyclic compounds⁴ and alkaloids⁵. In addition, enamines also serve as important precursors for synthesis of valuable therapeutic and biologically active molecules *e.g.* anticonvulsant⁶, antitumor⁷. Moreover, enamines also find use as useful intermediates for the preparation of aminoester⁸ including α , β -unsaturated aminoesters, peptides⁹ antimicrobial and antitumor¹⁰. Preparation of enamines from benzotriazole are well documented¹¹. Most commonly used methods for preparation of enamines involve catalytic amination of 1,3-diketones. Conventional catalysts employed are ceric ammonium nitrate

(CAN)¹², ZrOCl₂¹³, gold(I)/silver(I)¹⁴, Pd(PPh₃)₂Cl₂¹⁵, Indium TosMIC¹⁶. Preparation of enamines *via* ruthenium catalysed coupling of thioamides and α -diazocarbonyl compounds is also reported¹⁷. A rich source of enamines results either through base induced cleavage¹⁸ or reductive ring cleavage¹⁹ of suitably substituted isoxazoles along with samarium diiodide assisted²⁰ isoxazole ring opening. Benzotriazole and 2,2,4-trimethyl-2-oxazoline have found applications as strong acylating agents for metalated ketimine acylation leading to the formation of enamines in high yield²¹. Catalytic amination of 1,3- diketones producing N-substituted enamines, however, has some serious limitations for large scale preparations in terms of. high reaction time, temperature, catalyst cost and loading. Regio and chemoselective preparation of enamines could only be achieved with symmetrical 1,3-diketones²² or 1,3-dicarbonyl compounds having substantially different carbonyl reactivity²³.

Enamides, like enamines, are stable enamine surrogates and provide key intermediates for the synthesis of small but complex nitrogen containing heterocycles and display a fine balance of stability

and reactivity leading to their increasing multiple uses in organic reactions and synthesis²⁴. Preparation of enamides generally involves reductive acylation of oximes and ketoximes²⁵. Substituted 3-aminoquinolines were synthesised from ethyl N-nivaloyl-3-aminocrotonate²⁶.

Since enamines display pronounced ambident properties in C=C-N atom triad, one could envisage a very simple synthetic protocol for preparation of enamines or enamides from a common precursor by reacting enamines with acid chlorides provided N,C site selectivity in the triad is ensured. In the past, following this strategy we successfully developed²⁷ a highly regioselective preparation of enamines and enamides in excellent yields by reacting 3-aminocrotonitrile **1b** with acid chlorides. Initially, the reaction was carried without an added organic base when polymerization of **1b** was found to occur while use of triethylamine resulted in the formation of acid anhydride. Use of pyridine as an added organic base offered the best results. Saturated acid chlorides when reacted with **1b**, complete regioselectivity either at C-terminal or at N-terminal, was observed²⁷. Interestingly, reaction with aliphatic or aromatic α,β -unsaturated acid chlorides produced 3,4-dihydropyridin-(2*H*)-ones *via in situ* [3,3] sigmatropic rearrangement of the incipient enamides²⁸. In contrast, during acylation of **1b** with aromatic acid chlorides no such clear cut regioselectivity could be observed. Steric and electronic influence of an aromatic nucleus on the regio or stereochemical outcome in acylation of enamines is well recognized. Preference for terminal selectivity appears to be largely dependent on (i) choice of aliphatic/aromatic acid chlorides, (ii) position and nature of the substituents (EDG/EWG) and (iii) nature of added organic base.

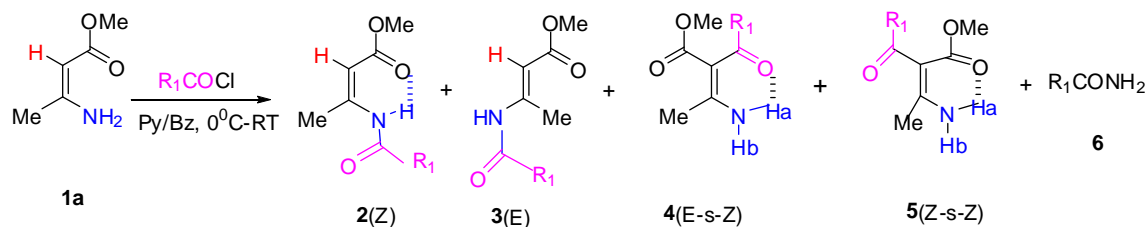
Easy excess to α -enaminoes in high yields allowed us to develop, for the first time, a regiospecific general synthesis of contiguously

substituted 1,2-azoles *i.e.* pyrazoles²⁹, isoxazoles³⁰ and isothiazoles³¹ from a common precursor.

EWG variants present in the examine moiety is known to exert strong influence in terminal site selection during acylation³². Encouraged by earlier success in ensuring regioselectivity in N,C-acylation of 3-aminocrotonitrile **1b**, the present investigation was undertaken with methyl 3-aminocrotonate (**1a**) in order to ascertain (a) relative efficacy of this system pertaining to useful synthetic applications and (b) to compare the derived results *vis-à-vis* with **1b**. Accrued information is expected to provide an insight to the preferred regio and stereoselectivity in N,C-acylation of these enamines *e.g.* **1a** and **1b** (Scheme I). To the best of our knowledge, till now, no such comparative study on the regio- and stereoselectivity in N,C-acylation of enaminoesters **1a** and enaminoitrile **1b** is reported or compiled. The present work reports the results of this investigation.

Results and Discussions

Early researchers reported^{2b,c,d,h,33} some preliminary work on acylation of more commonly used ethyl 3-aminocrotonate. However, lack of any systematic investigation on the regioselectivity in N,C-acylation of methyl 3-aminocrotonate (**1a**) prompted us to undertake this work. In the present study, acid chlorides used for acylation of **1a** were classified under the following heads: (i) aliphatic straight and branched-chain aliphatic acid chlorides (ii) acid chlorides of substituted acetic acid (iii) aromatic acid chlorides with or without substituent(s) and (iv) α,β -unsaturated acid chloride. Assignment of structure for the derived acylated products of **1a** are expected to be quite complex. Theoretically, four stereoisomers could result and in some cases formation of amide was also reported (Scheme I). In view of regio- and stereochemical complexity associated with the structure of the reaction products, successful



R₁ = a) CH₃, b) CH₂CH₃, c) CH(CH₃)₂, d) CHCl₂, e) CH₂OC₆H₅, f) CH₂OC₆H₃Cl₂(2,4), g) Ph, h) C₆H₄Cl(o), i) C₆H₄Cl(m), j) C₆H₄Cl(p), k) = C₆H₅CH=CH

Scheme I

application of this strategy in synthesis rests entirely on unambiguous structural assignment. Thankfully, acylated regio- and stereoisomers can easily be differentiated, identified and unequivocal assignment of the structure of the regio/stereoisomers could be achieved from extensive NMR spectral analysis (Experimental). Presence of C- and N-acylated products in the reaction mixture is characterised by appearance of three broad signals due to the presence of two sets of NH protons. The chelated NH signal for the N(Z)-isomer, secured by an intramolecular hydrogen bond between NH and C=O group, appears at a very low field (δ 11-13 ppm) whereas for the C(E)-isomer, the -NH proton signal appears at δ 7.5-8.5ppm. The ratio of the regio/stereoisomers present in the reaction mixture can also be easily determined from the integration values of C-Me signals for C- and N- acylated products. For the chelated Z-isomer, the shift for methyl protons is about 0.1 ppm down field and the vinylic hydrogen is about 1.9 ppm upfield as compared to the E-isomer. Shift differences are also observed in

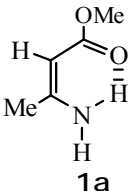
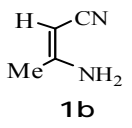
^{13}C NMR spectra³³ especially signals for those of C-2, C-3 and C-4.

(a) Acylation of methyl 3-aminocrotonate **1a** with straight and branched-chain aliphatic acid chlorides

In our study acylation was conducted by addition of acid chlorides of acetic acid and propionic acid into methyl 3-aminocrotonate (**1a**) in benzene in the presence of pyridine at 0°C and the reaction mixture was allowed to attain room temperature when only (Z)-enamides **2a** and **2b** were obtained in excellent yields (Scheme I, Table I). Enamide **2a** was also prepared³⁴ from **1a** by reacting with refluxing acetic anhydride.

Interestingly, reaction of these acid chlorides with **1b** showed complete reversal of site selectivity producing only C-acylated compounds^{27a}. When acylation of **1a** was extended to branched-chain aliphatic acid chloride namely acid chloride of isobutyric acid, a colorless liquid was obtained. (TLC and GC showed the presence of two compounds

Table I — N,C- acylation of **1a** and **1b** with aliphatic and aromatic acid chlorides (R_1COCl): Comparison of preference for regio- and stereoisomers

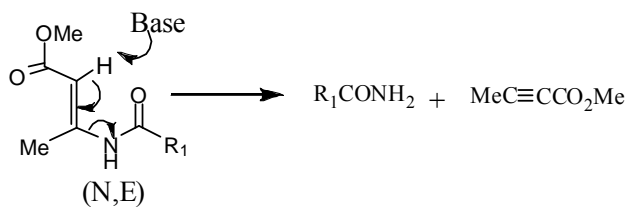
Entry No.	R_1COCl		Yield (%)		Yield (%) Lit ²⁷
		1a		1b	
		Product (N,C)		Product (N,C) ²⁷	
1	a) $\text{R}_1 = \text{CH}_3$	2a (N, Z) ³⁴	72%	(C, Z)	70%
2	b) $\text{R}_1 = \text{CH}_2\text{CH}_3$	2b (N, Z)	70%	(C, Z)	77%
3	c) $\text{R}_1 = \text{CH}(\text{CH}_3)_2$	2c (N, Z)	75%	(N, E)	78%
4	d) $\text{R}_1 = \text{CHCl}_2$	4d (C, E-s-Z)	80%	(C, Z)	71%
5	e) $\text{R}_1 = \text{CH}_2\text{OC}_6\text{H}_5$	2e (N, Z)	42%	(C, Z)	85%
		4e (C, E-s-Z)	35%		
		5e (C, Z-s-Z)	14%		
6	f) $\text{R}_1 = \text{CH}_2\text{OC}_6\text{H}_3\text{Cl}_2(2,4)$	2f (N, Z)	40%	(C, Z)	85%
		4f (C, E-s-Z)	32%		
		5f (C, Z-s-Z)	20%		
7	g) $\text{R}_1 = \text{Ph}$	2g (N, Z)	50%	(C,Z& N, E)	80%
		6g	20%		
8	h) $\text{R}_1 = \text{C}_6\text{H}_4\text{Cl} (o)$	2h (N, Z)	70%	(N, E)	71%
9	i) $\text{R}_1 = \text{C}_6\text{H}_4\text{Cl} (m)$	2i (N, Z)	69%	(N, E)	70%
		4i & 5i	10%		
10	j) $\text{R}_1 = \text{C}_6\text{H}_4\text{Cl} (p)$	(C, E & C,Z)			
		2j (N, Z)	60%	N,E& C, Z	74%
		4j & 5j	15%		
		(C, E & C, Z)			

($R_t = 3.165$ min; 82%) and ($R_t = 3.255$ min; 17%). Column chromatography (4% ethyl acetate – pet. ether) afforded the *Z*- isomer of the *N*-acylated product **2c** along with a small amount of amide **6c** resulting from **3c**. The suggested mechanism is depicted in Scheme II. This exclusive preference for *N*-terminal selectivity was in agreement with the result obtained previously when 3-aminocrotononitrile **1b** was reacted with isobutyryl chloride²⁷ (Table I, Scheme II).

(b) Acylation of methyl 3-aminocrotonate **1a** with substituted acetyl chlorides

In order to get further insight into site selection priority in *N,C*-acylation, substituted acetyl chlorides, in the presence of pyridine, were reacted with **1a**. Dichloroacetyl chloride afforded exclusively the *C*-acylated (*E-s-Z*) compound **4d** in high yield (80%) (Table I). It was reported³⁴ that reaction of amines with dichloroacetyl chloride in the presence of triethylamine prefers *N*-acylation producing dichloroacetamido *via* dichloroketene $\text{Cl}_2\text{C}=\text{O}$ which reacted with the more nucleophilic nitrogen centre³⁵. This observation once more highlights the imperative importance of the nature of the added organic base in *N,C*-site selectivity.

Phenoxyacetyl chloride and 2,4-dichlorophenoxyacetyl chloride, on the other hand, provided a complex mixture of *C*-and *N*-acylated products as revealed from examination of ¹H NMR spectrum of the crude reaction mixture. Pure compounds were isolated by column chromatography and were subjected to exhaustive spectral analyses. Both phenoxyacetyl chloride and 2,4-dichlorophenoxyacetyl chloride were found to produce *N*-acylated product and a pair of stereoisomeric *C*-acylated compounds. Thus, for phenoxyacetyl chloride, these were **2e** (*N,Z*; 42%), **4e** (*C,E-s-Z*; 14%) and **5e** (*C,Z-s-Z*; 35%) whereas 2,4-dichlorophenoxyacetyl chloride produced **2f** (*N,Z*; 40%), **4f** (*C, E-s-Z*; 20%) and **5f** (*C, Z-s-Z*; 32%). (Table I). Gross structure of **4f** and **5f** could easily be ascertained from their mass spectra (317.1M^+) and



Scheme II

elemental analyses. However, fine structure of the *C*-acylated products could only be established through extensive analysis of the NMR spectra including 2D-NMR(ROE) experiments, results of which correlate nicely with the assigned configuration.

The structure of *E-s-Z* and *Z-s-Z* isomer of *C*-acylated product was unequivocally proved by 2D-NMR (ROE). Further, *Z*-isomer can easily be differentiated from *E*-isomer as its chelated NH proton signal appears at a much low field (δ 10.48-10.68 ppm) compared to NH proton signal for *E*-isomer appearing at δ 9.77-9.87 ppm.

(c) Acylation of methyl 3-aminocrotonate (**1a**) with aromatic acid chlorides

Acylation of **1a** was further extended to aromatic acid chlorides (Table I). Thus, benzoyl chloride on reacting with **1a** in the presence of pyridine afforded, after column chromatography, two products. Spectral analysis showed the major product being (*Z*)-enamide **2g** and the minor one was found to be benzamide **6g** resulting from **3g** (Scheme II). Acylation of **1a** when carried with isomeric chlorobenzoyl chlorides gave interesting results. *o*-Chlorobenzoyl chloride showed unique preference for *N*-terminal selection producing only the *Z*-enamide **2h**, while reaction with acid chlorides of *m*- and *p*-chlorobenzoic acid gave a mixture of regio- and stereoisomers namely **2i** (*N,Z*), **4i** (*C, E-s-Z*), and **5i** (*C, Z-s-Z*) and **2j** (*N, Z*), **4j** (*C, E-s-Z*) and **5j** (*C, Z-s-Z*) respectively of which *Z*-isomers predominate (Table II). The pair of *C*-acylated products were found to be present as an inseparable mixture (1:1) of stereoisomers as ascertained from ¹H-NMR spectral analyses.

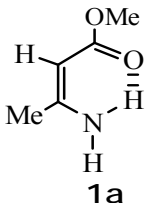
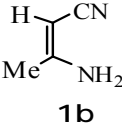
(d) Acylation of **1a** with α, β - unsaturated acid chlorides (cinnamoyl chloride)

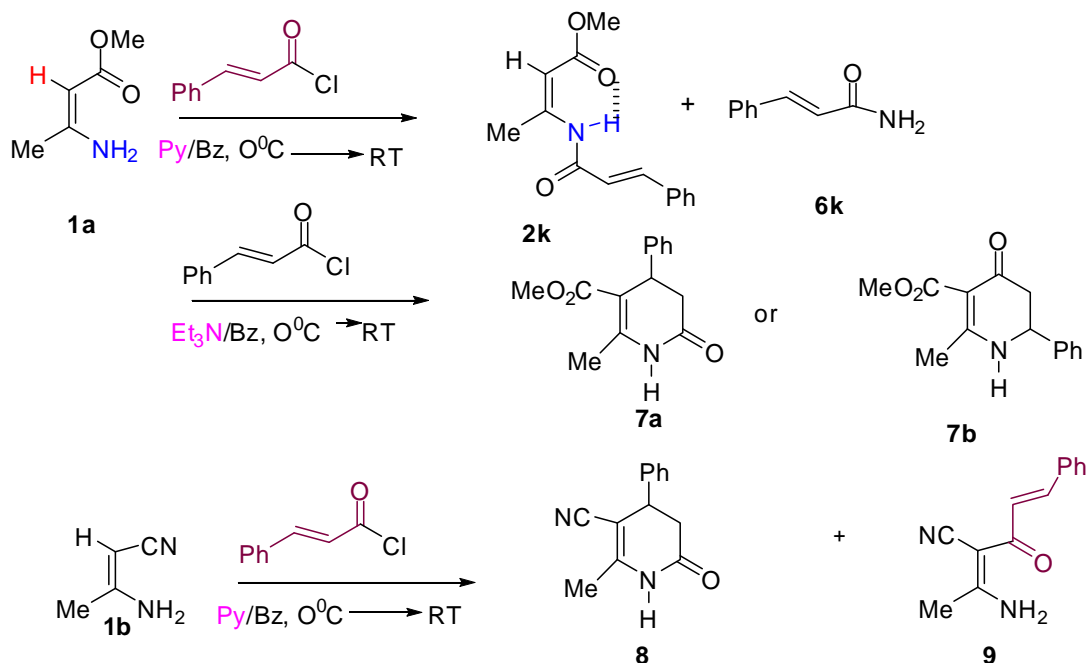
Our earlier work²⁸ showed that enamionitrile **1b** when reacted with α, β - unsaturated aliphatic or aromatic acid chlorides in the presence of triethylamine afforded pure 3,4-dihydropyridin-2(1H)-one **8** as the only product in high yield. It is pertinent to mention that Benary² reported formation of a mixture (1:1) of *C*-and *N*-acylated compounds when **1b** was reacted with cinnamoyl chloride in the presence of pyridine. We reinvestigated³⁶ this reaction under Benary condition and isolated compounds **8** and *C*(*Z*)-acylated enamionitrile **9** but could not detect (¹H NMR) any trace of *N*-acylated isomer in the reaction mixture. Benary designated *N*-acylated product was thus found to be dihydropyridone **8** and not the free enamide.

In order to ascertain if there be any difference in preferential C,N-site selectivity in acylation of enaminoester *vis-à-vis* enaminonitrile, methyl 3-aminocrotonate **1a** was initially reacted with cinnamoyl chloride in the presence of pyridine, the reaction mixture showed presence of two compounds (TLC; 1:4 ethyl acetate – petether). ¹H NMR spectral analysis of the pure materials (column chromatography) showed these to be the N(Z)-acylated compound **2k** and cinnamamide **6k** (Scheme II). Product composition of this reaction is quite revealing when compared with the reaction products obtained earlier with **1b**. Formation of **2k** along with **6k**, clearly a hydrolysed by-product of **3k**, demonstrates exclusive preference for N-acylation

in **1a**. Complete absence of dihydropyridone in the reaction mixture suggests that only E-enamide and not Z-enamide participates in its formation. This conclusion was further supported by the fact that Z-enamide even failed to induce cyclization in refluxing diphenyl ether. However, when pyridine was replaced by triethylamine as an added organic base, a highly crystalline material in high yield was obtained as the sole product. Spectral analyses (UV, IR, ¹H NMR, MS) indicated gross structure of this compound to be either 3,4-dihydropyridin-2(1H)-one **7a** or 3,4-dihydropyridin-4(1H)-one **7b** (Scheme III). Since these two systems are vinylogous. UV, IR and ¹H NMR data could not be used for unambiguous structural assignment³⁷.

Table II — Acylation of **1a** and **1b** with unsaturated acid chloride in presence of pyridine and triethylamine

Base		Yield (%)	m.p. (°C)		Yield (%) ²⁸	m.p. (°C) ²⁸
	Product			Product ²⁸		
Pyridine	2k	30	70-72	8	38%	196-197
Et ₃ N	6k	60	148-150	9	62%	189
	7a	75	180-182	8	80%	189



Scheme III

Mechanistically, **7a** could result *via in situ* [3.3] sigmatropic rearrangement of the intermediary N(E)-acylated isomer **3k**. However, as observed³⁶ previously with **1b**, C-acylated enaminonitrile **9** failed to undergo intramolecular Michael addition in refluxing diphenyl ether to produce 3,4-dihydropyridin-4(1H)-one **10** (Scheme IV). Thus, it was quite apparent that 3,4-dihydropyridin-2(1H)-one **7a** and not 3,4-dihydropyridin-4(1H)-one **7b** was formed in this reaction (Scheme IV). This conclusion was further supported^{38,39} by ¹³C NMR spectral analysis of compound **7a** wherein signals appearing at δ 171.27 (amide C=O), 167.72 (ester C=O) and 38.08 (C-4) ppm unequivocally supports the fine structure in favour of **7a**.

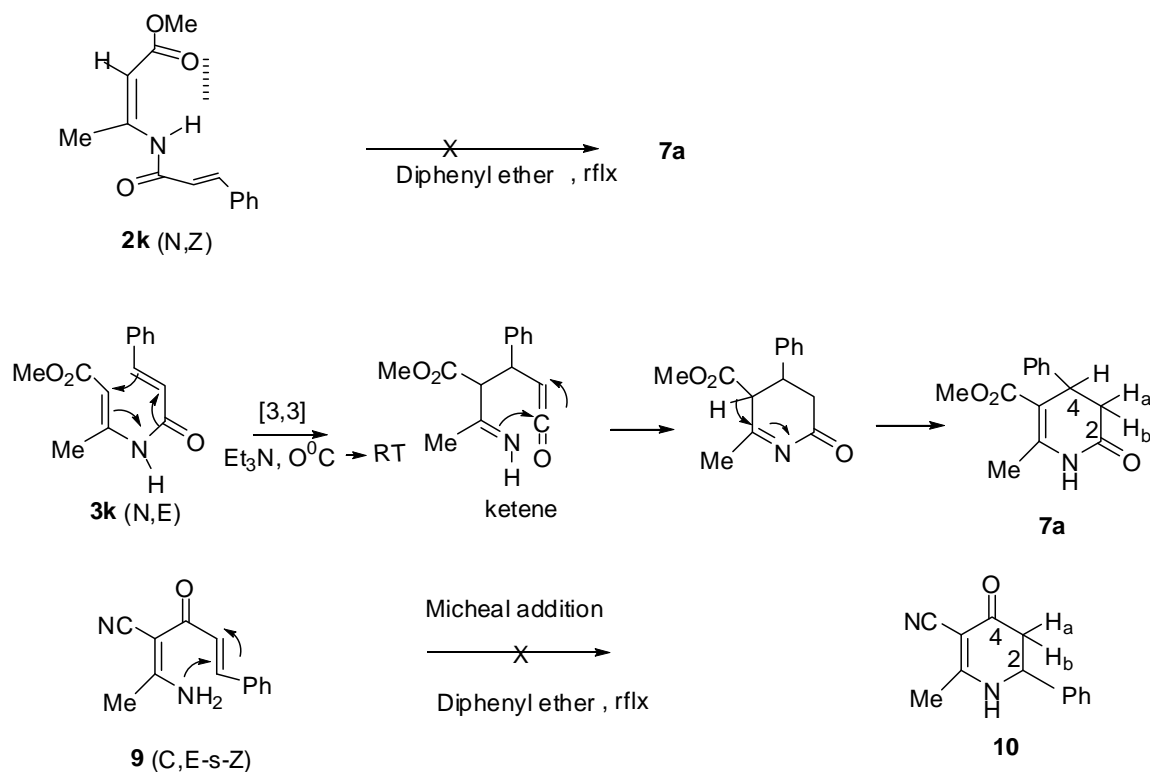
Plausible explanation for regioselectivity in C, N-acylation

Regioselectivity in C, N-acylation of enamines depends largely among others on the choice of the reacting acid chlorides and the added organic base. According to principle of least nuclear motion (PLNM) concept⁴⁰ less reorganisation is needed for attack at N-site of the enamines. This preference for

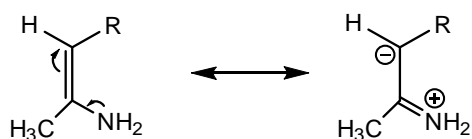
N-terminal is also supported from 'Hoz effect'⁴¹ which predicts lower intrinsic barriers for attack at the atom further right in the periodic table. In view of these observations, one may qualitatively assume that N-attack is intrinsically preferred *i.e.* acylation of enamines is expected to give N-acylated products.

Examination of the results obtained with **1a** and **1b** reveals some striking features with regard to preference for regio and stereoselectivity in N,C-acylation. Acyl chlorides, the added organic base and reaction conditions remaining same, it was found that substituent variants R in enamines tend to show distinct preference for site selection. Such unique site preference in N,C-acylation in these systems may be explained from the stability of their zwitterionic structure.

Between -CN and -CO₂Me groups, -CN has more pronounced electron withdrawing effect than -CO₂Me and because of this, zwitterionic form is more stabilized in case of **1b** (Figure 1). Acylation thus occurs, in most of the cases studied, preferentially at C-nucleophilic centre rather than nucleophilic free N centre of **1b** (Exception with isobutyryl chloride (exclusively N-acylation), benzoyl and isomeric



Scheme IV



1a R = -CO₂Me, **1b** R = -CN,

Figure 1

chlorobenzoyl chloride (mixture of C&N)) whereas preferential N-acylation occurs in case of **1a** (except dichloroacetyl chloride (exclusively C-acylation) and phenoxy and dichlorophenoxyacetyl chloride (1:1 N & C), isomeric chlorobenzoic acid (10-15% C-acylation)).

Conclusion

The present study highlights the importance of the choice of the enamines as regio- and stereoselectivity in N,C-acylation is found to be largely dependent on their properties.

This study further demonstrates that site selection in N,C-acylation, among other factors, is significantly dependent on the character of the added organic base. In our investigation we found that use of pyridine offered the best results. Use of triethylamine as an added organic base resulted in poor yields of the acylated products either due to polymerisation of the enamine or formation of the acid anhydride. Contrary to this observation, reaction of α,β -unsaturated acid chlorides with enamines **1a** and **1b** in the presence of triethylamine as an added organic base produced the best results in terms of regioselectivity and yields, providing an excellent route for regiospecific preparation of contiguously substituted 3,4-dihydropyridin-2(1H)-ones in a clean and high yielding reaction.

N(Z)-enamide **2k** under refluxing diphenyl ether failed to cyclize to form **7a**. Mechanistically this observation is extremely significant. Failure of N(Z)-stereoisomer to undergo cyclization clearly demonstrates that only N(E)-stereoisomer participates in (3,3)-sigmatropic rearrangement leading to formation of **7a**. Triethylamine, being a stronger amine probably pushes the equilibrium towards transient E-enamide.

A close examination of ¹H NMR spectral data of the acylated products obtained from **1a** revealed that N-acylated products exist in Z-configuration only. The C-acylated products, on the other hand, were found to

be present as a mixture of stereoisomers (Z, E), but with a clear preference for E-isomer. Comparison of the results obtained in N, C-acylation with **1a** and **1b** clearly demonstrates that choice of enaminonitrile **1b** rather than enaminoester **1a** would be more attractive as far as preparation of enaminones are concerned (Table I and Table II). This unique C-selectivity of **1b** is confined to aliphatic acid chlorides only. No such clear cut C-terminal preference was observed with aromatic acid chlorides. In view of simplicity of reaction, regioselective acylated products and high yields in N,C-acylation, enaminoester **1a** and enaminonitrile **1b** score over other primary enamines. Since ester and nitrile groups are chemically interconvertible use of **1b** eliminates the need for chromatographic separation of regio and stereoisomers formed in acylation with enaminoester **1a**.

N- and C-acylated enaminoesters and enaminonitriles have found extensive applications in synthesis, biological and pharmaceutical study. In view of the simplicity and high yields in N,C-acylation, methyl 3-aminocrotonate **1a** and 3-aminocrotononitrile **1b** score over other enamines in terms of preparation of regio- and stereoisomers.

In conclusion, this study for the first time, explored the comparative N,C-terminal preference of methyl 3-aminocrotonate (**1a**) and 3-aminocrotononitrile (**1b**). Since ester and nitrile groups are chemically interconvertible to many other useful functional groups, **1a** and **1b** bear complimentary relationship.

Experimental Section

Materials and Methods

Yields are given on the chromatographically pure compounds. Boiling points (bp) or melting points (mp) are uncorrected and measured in open capillary method. Solvents and reagents were purchased from Sigma-Aldrich and were purified by conventional literature methods. Thin-Layer Chromatography (TLC) was carried on precoated GF₂₅₄ TLC plates, flash chromatography (FC) was carried on silica gel (60-120 mesh). Gas chromatography (GC) was carried out by injecting samples in dichloromethane (DCM) through HP-1 and GC port INNOWAX capillary column, FID detector N₂ as carrier gas and maintaining the oven temperature at 40°C and then programmed to 220°C at 15°C/min in Agilnet 6890N instrument, IR spectra were recorded either neat or in KBr matrix on Hitachi 270-30 and Perkin Elmer, model spectrum-1 spectrometers. Ultraviolet spectra

in ethanol unless specified otherwise were recorded on Hitachi U-2000. NMR spectra in CDCl_3 or $\text{DMSO}-d_6$ were run on Bruker AC-200, Bruker DPX-400, Bruker Avance 400, Spect-400 and drx 500 MHz instruments. Tetramethylsilane (TMS) was used as an internal standard, δ values are reported in ppm, J values in Hertz. ^{13}C NMR assignments are derived from heteronuclear single quantum correlation (HSQC) and heteronuclear multiple bond correlation (HMBC) experiments. Mass spectra (m/z ; rel%) were determined in Hitachi RMU 6L, JEOL JMS 600, Thermo Finnigan LCQ DUO spectrometers. Elemental Analyses were performed in Perkin-Elmer 240C elemental analyser.

General procedure for the preparation of (Z)-methyl (3-alkylamido)-but-2-enoates, (Z)-methyl (3-arylamido)-but-2-enoates and (Z)-and (E)-methyl 3-amino-2-acyl but-2-enoates and (Z)-and (E)-methyl 3-amino-2-aroil but-2-enoates

To a magnetically stirred solution of methyl 3-aminocrotonate (1.15g, 0.01m), pyridine (0.03m) in dry benzene (15 mL) was added drop wise, freshly distilled acid chloride (0.01m) in dry benzene (10 mL) under ice-cold water. The reaction mixture was poured on to ice water on attaining ambient temperature. The mixture was extracted with ethyl acetate (3×25 mL). The organic layer was sequentially washed with cold (2N) hydrochloric acid solution (2×15 mL) to remove excess pyridine, saturated sodium bicarbonate solution until neutral and finally with brine. The organic layer was then dried over anhydrous sodium sulphate. Removal of the solvent afforded solid materials which on crystallization from a suitable solvent furnished pure acylated product **2a-2c**, **2e-2j** and **4d-4f**, **4i**, **4j** and **5e**, **5f**, **5i** and **5j**.

Preparation of (Z)-methyl 3-acetamido-but-2-enoate, 2a: White needle-shaped crystals. Yield 72%. m.p. 36°C. IR (KBr): 3584, 2470, 2306, 1719, 1618, 1552, 1436, 1255. UV (EtOH), λ_{max} in nm (ϵ): 340 (1401), 267 cm^{-1} (7217); ^1H NMR ($\text{DMSO}-d_6$): δ 2.10 (3H, s, CH_3), 2.30 (3H, s, $\text{C}=\text{CH}_3$), 3.70 (3H, s, OCH_3), 5.05 (1H, s, $\text{C}=\text{CH}$), 10.90 (1H, br, NH); ^{13}C NMR ($\text{DMSO}-d_6$): δ 21.33 (C-4), 24.83 (COCH_3), 50.84 (OCH_3), 95.36 (C-2), 154.65 (C-3), 168.53 (C=O), 168.55 (NHCO); MS: m/z (%) 157 (26) [M^+], 115 (51), 84 (100), 57 (23). Anal. Found: C, 53.78; H, 7.09; N, 8.79. Calcd for $\text{C}_7\text{H}_{11}\text{NO}_3$: C, 53.50; H, 7.05; N, 8.91%.

Preparation of (Z)-methyl 3-(propionamido)-but-2-enoate, 2b: Sugar-cube shaped crystals. Yield 70%. m.p. 48°C. IR (KBr): 3516, 2990, 2916, 2460, 2306, 1719, 1617, 1438, 1391, 1336, 1262 cm^{-1} ; UV (EtOH), λ_{max} in nm (ϵ): 338 (2619), 271 (10, 710); ^1H NMR (CDCl_3/TMS): δ 1.20 (3H, t, CH_2CH_3), 2.37 (3H, s, $\text{C}=\text{CH}_3$), 2H, q, CH_2CH_3), 3.70 (3H, s, OCH_3), 4.90 (1H, s, $\text{C}=\text{CH}$), 11.12 (1H, br, NH); ^{13}C NMR (CDCl_3/TMS): δ 9.04 (CH_2CH_3), 21.91 (C-4), 31.16 (CH_2CH_3), 50.86 (OCH_3), 95.67 (C-2), 155.23 (C-3), 169.45 (C=O), 172.59 (NHCO); MS: m/z (%) 171 [M^+] (32.5), 115 (75), 84 (100), 57 (90). Anal. Found: C, 56.38; H, 7.62; N, 8.23. Calcd for $\text{C}_8\text{H}_{13}\text{NO}_3$: C, 56.13; H, 7.65; N, 8.18%.

Preparation of (Z)-methyl 3-(isobutyramido)-but-2-enoate, 2c: Colourless liquid. Yield 75%. b.p. 65-66°C /0.6mm Hg; IR (KBr): 3254, 2964, 1711, 1624, 1477, 1440, 1384, 1252 cm^{-1} ; UV (EtOH), λ_{max} in nm (ϵ): 339 (2524), 268 (10531); ^1H NMR (CDCl_3/TMS): δ 1.22 & 1.24 (2×3H, d, $J = 6\text{Hz}$, 2× CH_3), 2.39 (3H, s, $\text{C}=\text{CH}_3$), 2.53 (1H, m, $\text{CH}(\text{CH}_3)_2$), 3.70 (3H, s, OCH_3), 4.92 (1H, s, $\text{C}=\text{CH}$), 11.19 (1H, br, NH); ^{13}C NMR (CDCl_3/TMS): δ 19.18 ($\text{CH}(\text{CH}_3)_2$), 21.99 (C-4), 37.10 (CH), 50.93 (OCH_3), 95.89 (C-2), 155.48 (C-3), 169.54 (CO), 175.97 (NHCO). Anal. Found: C, 58.61; H, 8.13; N, 7.61. Calcd for $\text{C}_9\text{H}_{15}\text{NO}_3$: C, 58.37; H, 8.16; N, 7.56%.

Preparation of (E)-methyl 3-amino-2-(2,2-dichloroacetyl)but-2-enoate, 4d: White crystals. Yield 80%. m.p. 64°C. IR (KBr): 3246, 3132, 1699, 1588, 1477, 1440, 1371, 1289 cm^{-1} ; UV (EtOH), λ_{max} in nm (ϵ): 301 (15, 730), 245 (13,610). ^1H NMR (CDCl_3/TMS): δ 2.39 (3H, s, $\text{C}=\text{CH}_3$), 3.80 (3H, s, OCH_3), 6.47 (1H, br, NH_b), 7.03 (1H, s, CHCl_2), 11.10 (1H, br, NH_a); ^{13}C NMR (CDCl_3/TMS): δ 24.66 (C-4), 51.63 (OMe), 69.61 (CHCl_2), 98.05 (C-2), 168.10 (ester C=O), 171.79 (C-3), 185.32 (keto C=O); MS: m/z (%) 225 (49) [M^+], 225.9 (35) [M^++1], 228 (10) [M^++3]. Anal. Found: C, 37.32; H, 4.03; N, 6.15; Calcd for $\text{C}_7\text{H}_9\text{NCl}_2\text{O}_3$: C, 37.19; H, 4.01; N, 6.19%.

Preparation of (Z)-methyl 3-(2-phenoxyacetamido)but-2-enoate, 2e: White needle-shaped crystals. Yield 42%. m.p. 88-89°C. IR (KBr): 3256, 1719, 1681, 1612, 1495, 1441, 1360, 1261 cm^{-1} ; UV (EtOH) λ_{max} in nm (ϵ): 267 (15711), 216 (4561); ^1H NMR (CDCl_3/TMS): δ 2.43 (3H, s, $\text{C}=\text{CH}_3$), 3.72 (3H, s, OCH_3), 4.53 (2H, s, CH_2), 5.02 (1H, s, $\text{C}=\text{CH}$), 6.98-7.73 (5H, m, Ar-H), 12.05 (1H,

br, *NH*); MS: *m/z* (%) 257 (35) [M^+], 218 (55), 95.9 (100), 83.9 (52). Anal. Found: C, 62.42; H, 6.10; N, 5.66. Calcd for $C_{13}H_{15}NO_4$: C, 62.65; H, 6.07; N, 5.62%.

Preparation of (*E*)-methyl 3-amino-2-(2-phenoxyacetyl)but-2-enoate, 4e: White flakes. Yield 35%. m.p 112-114°C. IR (KBr): 3272, 1678, 1598, 1448, 1433, 1286, 1220, 1123 cm^{-1} ; UV (EtOH), λ_{max} in nm (ϵ) 263 (14987), 214 (5219); 1H NMR ($CDCl_3/TMS$): δ 2.30 (3H, s, $C=CH_3$), 3.74 (3H, s, OCH_3), 4.95 (2H, s, CH_2), 6.82-7.50 (5H, m, Ar-*H*), 8.69 (1H, br, NH_b), 10.48 (1H, br, NH_a); MS: *m/z* (%) 257 [M^+], 218.1 (52), 106.9 (100), 95.9 (93), 84 (45). Anal. Found: C, 62.39; H, 6.11; N, 5.69. Calcd for $C_{13}H_{15}NO_4$: C, 62.65; H, 6.07; N, 5.62%.

Preparation of (*Z*)-methyl 3-amino-2-(2-phenoxyacetyl)but-2-enoate, 5e: White crystals. Yield 14%. m.p. 96-97°C. IR (KBr): 3422, 2944, 1690, 1599, 1564, 1548, 1487, 1433, 1343, 1223 cm^{-1} ; UV (EtOH), λ_{max} in nm (ϵ): 289 (8221), 240 (5323); 1H NMR ($CDCl_3/TMS$): δ 2.42 (3H, s, $C=CH_3$), 3.69 (3H, s, OCH_3), 4.52 (2H, s, CH_2), 6.58 (1H, br, NH_b), 6.84-7.37 (5H, m, Ar-*H*), 9.77 (1H, br, NH_a); MS: *m/z* (%) 257 [M^+] 218.1 (52), 106.9 (100), 95.9 (93), 84 (45). Anal. Found: C, 62.33; H, 6.09; N, 5.65. Calcd for $C_{13}H_{15}NO_4$: C, 62.65; H, 6.07; N, 5.62%.

Preparation of (*Z*)-methyl 3-(2-(2,4-dichlorophenoxy)acetamido)but-2-enoate, 2f: White flakes. Yield 40%. m.p 109-110°C. IR (KBr): 3252, 1707, 1688, 1637, 1491, 1436, 1391, 1378, 1294, 1262 cm^{-1} ; UV (EtOH), λ_{max} in nm (ϵ): 268 (14425), 232 (8730); 1H NMR ($CDCl_3/TMS$): δ 2.36 (3H, s, $C=CH_3$), 3.61 (3H, s, OCH_3), 4.83 (2H, s, CH_2), 5.15 (1H, s, $C=CH$), 7.20-7.64 (5H, m, Ar-*H*), 11.49 (1H, br, NH); ^{13}C NMR ($CDCl_3/TMS$): δ 21.65 (C-4, Me), 50.99 (OMe), 68.30 (CH_2), 97.51 (C-2), 122.90, 125.79, 128.14, 129.58 (Ar-C), 152.49 (C-3), 166.66 (ester keto C=O), 168.04 (amide C=O); MS: *m/z* (%) 317.1 (37.49) [M^+], 282.1 (96.44), 253 (43.33), 175 (23.55), 156.1 (100), 142.1 (64.04), 110 (83.85), 96.1 (86.58), 84.1 (16.23), 69 (21.99), 55 (15.40). Anal. Found: C, 49.28; H, 4.15; N, 4.44. Calcd for $C_{13}H_{13}NCl_2O_4$: C, 49.08; H, 4.12; N, 4.40%.

Preparation of (*E*)-methyl 2-(2-(2,4-dichlorophenoxyacetyl)-3-amino-but-2-enoate, 4f: White flakes. Yield 32%. m.p 122-124°C. IR (KBr): 3344, 2953, 1656, 1623, 1584, 1477, 1435, 1390,

1297, 1237 cm^{-1} ; UV (EtOH), λ_{max} in nm (ϵ): 289 (12773), 236 (12004); 1H NMR ($CDCl_3/TMS$): δ 2.21 (3H, s, $C=CH_3$), 3.65 (3H, s, OCH_3), 5.05 (2H, s, CH_2), 6.84-7.54 (5H, m, Ar-*H*), 8.79 (1H, br, NH_b), 10.68 (1H, br, NH_a); ^{13}C NMR ($CDCl_3/TMS$): δ 22.75 (C-4), 50.75 (OMe), 72.11 (CH_2), 98.22 (C-2), 114.66, 121.90, 124.00, 127.82, 129.21 (Ar-C), 153.03 (C-3), 168.31 (ester C=O), 170.58 (keto C=O); MS: *m/z* (%) 316.1 (100) [$M-H$], 318.1 (65) [MH^++1]. Anal. Found: C, 49.28; H, 4.15; N, 4.44. Calcd for $C_{13}H_{13}NCl_2O_4$: C, 49.08; H, 4.12; N, 4.40%.

Preparation of (*Z*)-methyl 2-(2-(2,4-dichlorophenoxyacetyl)-3-amino-but-2-enoate, 5f: White granular crystals. Yield 20%. m.p 138-139°C. IR (KBr): 3391, 3071, 1706, 1644, 1515, 1481, 1436, 1389, 1295, 1266 cm^{-1} ; UV (EtOH), λ_{max} in nm (ϵ): 263 (14457); 1H NMR ($CDCl_3/TMS$): δ 2.32 (3H, s, $C=CH_3$), 3.59 (3H, s, OCH_3), 4.85 (2H, s, CH_2), 6.69 (1H, br, NH_b), 7.05-7.62 (5H, m, Ar-*H*), 9.87 (1H, br, NH_a); ^{13}C NMR ($CDCl_3/TMS$): δ 21.65 (C-4), 50.63 (OMe), 67.88 (CH_2), 99.09 (C-2), 115.12, 122.30, 125.01, 128.09, 129.50 (Ar-C), 151.46 (C-3), 167.14 (ester C=O), 167.77 (keto C=O). MS: *m/z* (%) 317.1 (18.50) [M^+], 282.1 (91.08), 258.1 (39.76), 175 (23.42), 156.1 (98.99), 142.1 (63.35), 110 (88.48), 96.1 (100), 84.1 (21.10), 68 (13.75), 55 (15.88). Anal. Found: C, 49.42; H, 4.15; N, 4.44. Calcd for $C_{13}H_{13}NCl_2O_4$: C, 49.08; H, 4.12; N, 4.40%.

Preparation of (*Z*)-methyl 3-(benzamido)but-2-enoate, 2g: White crystals. Yield 50%. m.p 45-47°C. IR (KBr): 3204, 2966, 1694, 1663, 1617, 1529, 1473, 1450, 1262 cm^{-1} ; UV (EtOH), λ_{max} in nm (ϵ): 293 (21002), 239 (19972); 1H NMR ($CDCl_3/TMS$): δ 2.40 (3H, s, $C=CH_3$), 3.60 (3H, s, OCH_3), 5.00 (1H, s, $C=CH$), 7.10-8.00 (5H, m, Ar-*H*), 11.20 (1H, br, NH); MS: *m/z* (%) 188 (100) [M^+-OMe], 242 (30) [M^++Na^+]. Anal. Found: C, 66.10; H, 5.70; N, 6.45. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39%.

Preparation of (*Z*)-methyl 3-(2-chlorobenzamido)but-2-enoate, 2h: White needle-shaped crystals. Yield 61%. m.p. 58-60°C. IR (KBr): 3250, 1709, 1670, 1630, 1430, 1263, 1183 cm^{-1} ; UV (EtOH), λ_{max} in nm (ϵ): 340 (4098), 278 (10288); 1H NMR ($CDCl_3/TMS$): δ 2.54 (3H, s, $C=CH_3$), 3.68 (3H, s, OCH_3), 5.05 (1H, s, $C=CH$), 7.34-7.60 (4H, m, Ar-*H*), 11.52 (1H, br, NH); ^{13}C NMR ($CDCl_3/TMS$): δ 22.11 (C-4), 51.14 (OMe), 97.63 (C-2), 127.09, 129.21, 130.66, 131.32, 131.71, 135.33 (Ar-C), 154.59

(C-3), 165.27 (ester C=O), 169.30 (amide C=O); MS: m/z (%) 254 (3) $[MH^+]$, 222 (33) $[M^+-OCH_3]$, 138.9 (100) $[C_6H_4COCl^+]$, 140.9 (34) $[C_6H_4COCl^++2]$. Anal. Found: C, 56.59; H, 4.79; N, 5.62. Calcd for $C_{12}H_{12}NClO_3$: C, 56.82; H, 4.77; N, 5.52%.

Preparation of (Z)-methyl 3-(3-chlorobenzamido)but-2-enoate, 2i: White crystals. Yield 69%. m.p. 75-76°C. IR (KBr): 3244, 3012, 1670, 1639, 1560, 1505, 1465, 1439, 1268, 1175 cm^{-1} ; UV (EtOH), λ_{max} in nm (ϵ): 284 (13435); 1H NMR ($CDCl_3/TMS$): δ 2.53 (3H, s, C=CH₃), 3.75 (3H, s, OCH₃), 5.07 (1H, s, C=CH), 7.41-7.98 (4H, m, Ar-H), 12.11 (1H, br, NH); ^{13}C NMR ($CDCl_3/TMS$): δ 22.03 (C-4), 51.30 (OMe), 97.45 (C-2), 125.24, 128.28, 130.08, 132.41, 135.41 (Ar-C), 155.23 (C-3), 163.96 (ester C=O), 169.86 (amide C=O); MS: m/z (%) 252 (68) $[M^+-1]$, 224 (100) $[M^++2-OCH_3]$, 274 (37) $[M^++Na^+]$. Anal. Found: C, 56.62; H, 4.80; N, 5.58. Calcd for $C_{12}H_{12}NClO_3$: C, 56.82; H, 4.77; N, 5.52%.

Preparation of (E)-methyl (2-m-chlorobenzoyl)-3-amino-but-2-enoate 4i & (Z)-methyl (2-m-chlorobenzoyl)-3-amino-but-2-enoate, 5i: White crystals. Yield 10%. m.p. 80-85°C. IR (KBr): 3386, 3058, 1670, 1607, 1493, 1371, 1257, 1169 cm^{-1} ; UV (EtOH), λ_{max} in nm (ϵ): 303 (11711), 211 (18226); 1H NMR ($CDCl_3/TMS$): δ 2.13, 2.37 (3H, s, C=CH₃), 3.34, 3.44 (3H, s, OCH₃), 5.44 (1H, br, NH_b), 5.88 (1H, br, NH_b), 7.28-7.72 (4H, m, Ar-H), 9.11 (1H, br, NH_a), 10.77 (1H, br, NH_a).

Preparation of (Z)-methyl 3-(3-chlorobenzamido)but-2-enoate, 2j: White shiny crystals. Yield 60%. m.p. 119-120°C. IR (KBr): 3216, 1618, 1480, 1465, 1439, 1265, 1171 cm^{-1} ; UV (EtOH), λ_{max} in nm (ϵ): 290 (18302); 1H NMR ($CDCl_3/TMS$): δ 2.52 (3H, s, C=CH₃), 3.74 (3H, s, OCH₃), 5.06 (1H, s, C=CH), 7.46 (2H, d, $J = 9$ Hz, Ar-H), 7.91 (2H, d, $J = 9$ Hz, Ar-H), 12.12 (1H, br, NH); ^{13}C NMR ($CDCl_3/TMS$): δ 22.01 (C-4), 51.25 (OMe), 97.20 (C-2), 129.04, 129.11, 132.29, 138.80 (Ar-C), 155.44 (C-3), 164.22 (ester C=O), 169.96 (amide C=O); MS: m/z (%) 222 (27) $[M^+-OCH_3]$, 224 (8) $[M^++2-OCH_3]$, 138.9 (100) $[C_6H_4COCl^+]$, 140.9 (32) $[C_6H_4COCl^++2]$. Anal. Found: C, 56.55; H, 4.79; N, 5.60. Calcd for $C_{12}H_{12}NClO_3$: C, 56.82; H, 4.77; N, 5.52%.

Preparation of (E)-methyl (2,4-chlorobenzoyl)-3-amino-but-2-enoate (4j) & (Z)-methyl (2-(4-chlorobenzoyl)-3-amino-but-2-enoate, 5j: White crystals. Yield 15%. m.p. 110-112°C. IR (KBr): 3270, 1685, 1588, 1438, 1284, 1193 cm^{-1} ; UV (EtOH), λ_{max} in nm (ϵ): 301 (10360), 245 (12738); 1H NMR ($CDCl_3/TMS$): δ 2.11, 2.37 (3H, s, C=CH₃), 3.34, 3.45 (3H, s, OCH₃), 5.28 (1H, br, NH_b), 5.71 (1H, br, NH_b), 7.31-8.04 (4H, m, Ar-H), 9.08 (1H, br, NH_a), 10.74 (1H, br, NH_a).

Preparation of (Z)-methyl 3-(cinnamido)but-2-enoate, 2k: White flakes. Yield 30%. m.p. 70-72°C. IR (KBr): 3266, 3116, 2190, 1617, 1481, 1442, 1325, 1243 cm^{-1} ; UV (EtOH), λ_{max} in nm (ϵ): 306 (19183); 1H NMR ($CDCl_3/TMS$): δ 2.50 (3H, s, C=CH₃), 3.75 (3H, s, OCH₃), 5.00 (1H, s, C=CH), 6.54 (1H, d, $J = 15$ Hz, HC=CHPh), 7.39-7.57 (5H, m, Ar-H), 7.62 (1H, d, $J = 15$ Hz, HC=CHPh), 11.42 (1H, br, NH); MS: 246 (5) $[MH^+]$, 268 (25) $[M^++Na^+]$. Anal. Found: C, 68.77; H, 6.19; N, 5.58. Calcd for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71%.

Preparation of methyl 1,2,3,4-tetrahydro-6-methyl-2-oxo-4-phenyl pyridine-5-carboxylate, 7a: White crystals. Yield 75%. m.p. 180-182°C. IR (KBr): 3218, 3102, 1686, 1625, 1492, 1453, 1379, 1318, 1287, 1206 cm^{-1} ; UV (EtOH), λ_{max} in nm (ϵ): 281 (15312); 1H NMR ($CDCl_3/TMS$): δ 2.37 (3H, s, C=CH₃), 2.63 (1H, d, $J = 16.08$ Hz, H_a), 2.85 (1H, dd, $J = 8.06$ Hz & 16.52 Hz, H_c), 3.60 (3H, s, OCH₃), 4.19 (1H, d, $J = 7.75$ Hz, H_b), 7.28 (5H, m, Ar-H), 8.11 (1H, br, NH); ^{13}C NMR ($CDCl_3/TMS$): δ 19.58 (6-Me), 38.09 (C-3), 38.44 (C-4), 51.83 (OMe), 107.37 (C-5), 127.06, 127.40, 128.97, 129.18, 129.41, 142.25 (Ar-C), 146.79 (C-6), 167.72 (C=O), 171.27 (C-2); MS: m/z (%) 245.1 (70) $[M^+]$, 213 (82), 186 (100), 157 (18), 131 (20), 115 (14), 77 (12). Anal. Found: C, 68.74; H, 6.20; N, 5.76. Calcd for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71%.

Acknowledgements

Professor V. A. Snieckus, Queen's University, Ontario, Canada and Dr. W. Froestl, A C Immune, Basel, Switzerland are profusely thanked for their help and encouragement. Financial assistance (AM) from Jadavpur University is gratefully acknowledged.

References

- Smith Michael B, March Jerry (2007), *Advanced Organic Chemistry: Reactions, Mechanism and Structure*, 6th edn, (Wiley-Interscience, New York) SBN 0-471-72091-7; (b) Clayen Jonathan, *Organic Chemistry* (Oxford University Press, Oxford) (2001) ISBN 0-19--50346-6; (c) *Enamines: Synthesis, Structure and Reactions*, 2nd edn, edited by Gibert Cook 1988 (Marcell Dekker, NY) (1988) ISBN 0-8247-7764-6.
- (a) Erian A W, *Chem Rev*, 93 (1993) 1991; (b) Benary E, *Chem Ber*, 42 (1909) 3912; (c) Benary E, Reiter F & Soenderop H, *Chem Ber*, 50 (1917) 65; (d) Benary E & Hosenfeld M, *Chem Ber*, 55 (1922) 3417; (e) Grob C A, *Helv Chim Acta*, 33 (1950) 1787; (f) Cimarelli C & Palmieri G, *Tetrahedron Asymmetry*, 5 (1994) 1455; (g) Nour M, Tan K, Jankowski R & Cave C, *Tetrahedron Asymmetry*, 12 (2001) 765; (h) Braibante M E F, Brainbante H T S, Costa C C & Martins D B, *Tetrahedron Lett*, 43 (2002) 8079; (i) Chuang C-P & Wu Y-L, *Tetrahedron*, 60 (2004) 1841; (j) Hendra F, Nour M, Baglin I, Morgant G & Cave C, *Tetrahedron Asymmetry*, 15 (2004) 1027.
- (a) Raslan Mohamed A & Omran A O, *J Heterocycl Chem*, (2015) June 26; DOI: 10. 1002/Jhet 2359; (b) Nagaraju V, Purnachandar D, Rao Mangina N S V M, Suresh S, Sridhar B & Karunakar G V, *Org Biomol Chem*, 13 (2015) 3011; (c) Liu Y Y, Zhou R & Wang J-P, *Synth Commun*, 43 (2013) 2475 (d) Govindh B, Diwakar B S & Murthy Y L N, *Org Commun*, 5 (2012) 105; (e) Saleh G M, Al-Monsari, Sheriff M, Mernant M A K & Elnagdi M H, *ARKIVOC*, (2009) (Xi) 1; (f) Nakamura I & Yammolo Y A, *Chem Rev*, 104 (2004) 2127; (g) Elassar A-Z A, El-Khair A A, *Tetrahedron*, 59 (2003) 8463.
- (a) Wang J-P, Cao S & Lin Y, *J Org Chem*, 80 (2015) 9028. (b) Abu Zaid A, Hassanian S & Ghozlan A S, *J Heterocycl* (c) Ahmed Abd El-Hammed H, *Int J Org Chem*, 4 (2014) 68; (d) Songsichan T, Promsuk J, Rukachais V & Kaeobamrung J, *Org Biomol Chem*, 12 (2014) 4571; (e) Wang C, Dong C, Kong L, Li Yanli & Li Yanzhong, *Chem Commun*, 50 (2014) 2164.
- (a) Li G, Watson K, Buokheet R W & Zhang Y, *Org Lett*, 9 (2007) 2043; (b) Calle N, Carlos L A, Ortega A G & Gonzalez-Nogel A M, *Tetrahedron*, 62 (2006) 611; (c) Nakamura I & Yamamolo Y, *Chem Rev*, 104 (2004) 2127.
- Michael J P, Konning C R, Hosken G D & Standbury T V, *Tetrahedron*, 57 (2001) 9635.
- (a) Haycock-Lewandoski S J, Wilder A & Ahmman J, *J Org Process Res Dev*, 12 (2008) 1094; (b) Eddington N D, Cox D S, Roberts R R, Butcher R J, Edafiogho I O, Stables J P, Cooke N, Goodwin A M, Smith C A & Scott K R, *Eur J Med Chem*, 37 (2002) 635 (c) Shen R, Porco J A Jr, *Org Lett*, 2(9) (2000) 1333.
- (a) Cimarelli C & Palmeiri G, *J Org Chem*, 61 (1996) 5557; (b) Cimarelli C, Palmier G & Volpine E, *Synth Commun*, 31 (2001) 2943.
- Beholz L G, Benovosky R, Ward D L, Bata N S & Still J R, *J Org Chem*, 62 (1997) 1033.
- Riyadh S M, *Molecules*, 16 (2011) 1834.
- (a) Katritzky A R, Barcock R A, Long Q-H, Balasubramanian M, Malhotra N & Greenhill J V *Synthesis*, 233 (1993); (b) Bartoli G, Cimarelli C, Palmieri G, Bosco M & Dalpozzo R, *Synthesis*, 895 (1990); (c) Gayon E, Szymczyk M, Gerard H, Vrancken E & Campagne J-M, *J Org Chem*, 77 (2012) 9205; (d) Liu Y, Zhou R & Wan J-P, *Synth Commun*, 43,(2013) 2475.
- Sridharan V, Avendano C C & Menendez J C, *Synlett*, (2007) 2133.
- Zhang Z H, Li T S & Li J J, *Catal Commun*, 8 (2007) 1615.
- Zhang M, Abdulkader A, Fu Y & Zhu C, *Molecules*, 17 (2012) 2812.
- Karpov A S & Muller T J J, *Synthesis*, (2003) 2815.
- Krishna P R & Sekhar E R, *Adv Synth Catal*, 350 (2008) 2871.
- Kodurit Z, Wang N D, Cannell Kooley G K, Lema T H, Miao K, Nguyen M, Frohock. B, Castaneda V, Scott H, Albinsen D & Hussaini S R, *J Org Chem*, 79 (2014) 7405.
- Alberola A, Antolfin F L, Gonzalez A M, Laguna M A & Pulido F J, *J Heterocycl Chem*, 23 (1986) 1035.
- Fogagnolo M, Giovannini P P, Guerrini A, Medicin A, Pedrini P & Colombi N, *Tetrahedron Asymmetry*, 9 (1998) 2317.
- Natale N R, *Tetrahedron Lett*, 23 (1982) 5009.
- Katritzky A R, Fang Y, Donkor A & Xu J, *Synthesis*, (2000) 2029.
- (a) Edafiogho I O, Moore J A, Farrar V A, Nicholson J M & Scott K R, *Pharm Sci*, 83 (1994) 79; (b) Valduga C J, Squizani A, Braibante H S & Braibante M E F, *Synthesis*, (1998) 1019; (c) Azzaro M, Geribaldi S & Videau B, *Synthesis*, (1981) 880.
- (a) Harrad M A, Outtouch R, Ali M A, Firdoussi L E, Karim A & Roucoux A, *Catal Commun*, 11 (2010) 442; (b) Liu Y Y, Zhou R & Wang J-P, *Synth Commun*, 2475 (2013); (c) Brown N M D & Nonhebel D C, *Tetrahedron*, 5655 (1968); (d) Singh R V & Tandon J, *J Prakt Chem*, 151 (1979); *Chem. Abstr*, 90 (1979) 214461.
- (a) Carbery D R, *Org Biomol Chem*, 3455 (2008); (b) Matsubara R & Kobashi T, *Acc Chem Res*, 41 (2008) 292; (c) Reddy G J, Latha D, Thirupathaiiah C & Rao K S, *Tetrahedron Lett*, 46 (2005) 301; (d) Negri G, Kascheres C & Kascheres A J, *J Heterocycl Chem*, 41 (2004) 461.
- (a) Volkov A, Tinnis F & Adolfsson H, *Org Lett*, 16 (2014) 680; (b) Tang W, Capacci A, Sarvastani M, Wei X, Yee N K & Senanayake C H, *J Org Chem*, 74 (2009) 9628; (c) Zhao H, Vandenbossche C P, Knoeing S G, Singh S P & Bakale R P, *Org Lett*, 10 (2008) 505; (d) Volkov A, Tinnis F & Adolfsson H, *Org Lett*, 16 (2014) 680.
- Bujok R, Kwast A, Cmoch P & Wrobel Z, *Tetrahedron*, 66 (2010) 698.
- (a) Mahalanabis K K, Sarkar M, Dutta Chowdhury S K & Chatterjee A, *J Indian Chem Soc*, 80 (2003) 1143; (b) Mahalanabis K K, Sarkar M, Dutta Chowdhury S K & Ghosal C R, *Indian J Chem*, 41B (2002) 1902.
- Dutta Chowdhury S K, Sarkar M, Roy Chowdhury S & Mahalanabis K K, *Synth Commun*, 26 (1996) 4233.
- Dutta Chowdhury S K, Sarkar M & Mahalanabis K K, *J Chem Res (s)*, 746 (2003).
- Mahalanabis K K, Dutta Chowdhury S K & Sarkar M, *J Chem Res (s)*, 78 (2006).
- (a) Mishra M, Dutta Chowdhury S K & Mahalanabis K K, *Synth Comm*, 36 (2004) 2681; (b) Mishra M & Mahalanabis K K, *Indian J Chem*, 40B (2007) 204.
- Kuthan V, *Collect Czech Chem Commun*, 34(10) (1969) 2942.

- 33 Shabana R, Rasmussen J B & Lawessen S O, *Bull Soc Chim Belg*, 90 (1981) 75.
- 34 (a) Lubell W D, Kitamura M & Noyori R, *Tetrahedron Asymmetry*, 2 (1991) 543.
- 35 (b) Zhu G, Chen Z & Zhang X, *J Org Chem*, 64 (1999) 6907.
- 36 Hazra B G, Pore V S & Maybhate S P, *Org Prep Proc Int*, 21 (1989) 355.
- 37 Mahalanabis K K, Sarkar M, Dutta Chowdhury S K & Bose S, *Indian J Chem*, 37B (1998) 1234.
- 38 Williams D H & Fleming I, *Spectroscopic Methods in Organic Chemistry* (McGraw Hill, New York) (1973).
- 39 Breitmeier E & Voelter M, *Carbon¹³ NMR Spectroscopy* (VCH, New York) (1987).
- 40 Elliel E L & Pietrusiewicz K M, *Topics in Carbon¹³ NMR Spectroscopy*, Chapter 3, edited by G C Lavy (Wiley Interscience, New York) (1979).
- 41 (a) Kornblum N, Larsen H O, Mooberry D D, Blackwood R K, Oliveto E P & Graham G E, *Chem Ind*, 443 (1955); (b) Hine J, *Adv Phys Org Chem*, 15 (1977) 1.
- 42 Mayr H, Breugst M & Ofial A R, *Angew Chem Int Ed*, 50 (2011) 6470.