One-pot conversion of β-aminocrotononitrile to secondary enaminonitriles including chiral ones — Application to synthesis

A. Chatterjee, M. Mishra, S.K. Dutta Chowdhury, and Kumar K. Mahalanabis

Abstract: A highly efficient one-pot conversion of β-aminocrotononitrile to secondary enaminonitriles including chiral ones is described. In contrast to β-aminocrotononitrile, some of these *N*-substituted β-enaminonitriles on reacting with acid chlorides show a unique preference for C-terminal selection allowing preparation of pyrazoles without separation of regioisomers. In addition, use of secondary enaminonitriles also provided access to pyrazoles that are not obtainable with primary enaminonitriles owing to an exclusive preference for *N*-terminal selection.

Key words: β-aminocrotononitrile, *N*-substituted enaminonitriles, regioselective, pyrazoles.

Résumé : On décrit une méthode unipot très efficace de conversion du β-aminocrotononitrile en énaminonitriles secondaires, y compris ceux de nature chirale. Contrairement à ce qui est observé avec le β-aminocrotononitrile, certains de ces β-énaminonitriles *N*-substitués réagissent avec les chlorures d'acides avec une préférence unique pour la position C-terminale, ce qui permet de préparer des pyrazoles sans avoir à séparer les régioisomères. De plus, l'utilisation d'énaminonitriles secondaires permet aussi d'accéder à des pyrazoles qui ne peuvent pas être obtenus à partir de l'énaminonitrile primaire en raison de la préférence exclusive pour la sélection *N*-terminale.

Mots clés : β-aminocrotononitrile, énaminonitriles *N*-substitués, régiosélective, pyrazoles.

[Traduit par la Rédaction]

Introduction

The chemistry of β-aminocrotononitrile is well-documented (1) and continues to remain an active area for further study. For some time now we have been engaged in systematic studies on the acylation reactions of β-aminocrotononitrile (**1**) with acid chlorides in the presence of an added organic base to evaluate preferences for regioselection (2–5) and to explore the utility of the derived products for synthesis of novel heterocyclic compounds (6–9). β-Acylenaminonitriles behave as masked 1,3-diketones and are considered to be useful intermediates (10) particularly in heterocyclic chemistry (11). Results reported from this laboratory on acylation reactions of primary enaminonitriles with acid chlorides although indicating a high degree of preference for terminal selection depending on the choice of acid chlorides used, nevertheless indicate that there is room to develop new routes to ensure exclusive acylation at the C-terminal particularly in those cases where either *N*-acylation occurred or a mixture of *C*- and *N*-acylated products were obtained. To realize this objective we decided to explore secondary enaminonitriles instead of **1** in our acylation study and to observe if there was any change in preference for terminal selection with regard to **1**. This contemplated study required preparation of a large number of secondary enaminonitriles in reasonably good yields under mild conditions. Several methods of preparation of *N*-substituted enaminonitriles are reported in the literature (12–17), but most of these employed indirect methods and thus are not suitable for a preparatory scale. Dedina et al. (16) reported three different procedures for the preparation of *N*-substituted-3-aminocrotononitrile: procedure A uses a solution of enaminonitrile and an amine in ethanol in an autoclave at 130–136 °C for 5–8 h. In procedure B, a solution of HCl (6 mol/L) in ethanol was added to a dioxane solution of enaminonitrile and amine and the mixture was heated for 5 to 6 h in a pressure tube at 120–140 °C. Procedure C involves heating a mixture of enaminonitrile and amine without any solvent. In our study we observed that the use of HCl or the absence of ethyl alcohol resulted in extensive polymerization of the enaminonitrile itself and the yield of the secondary enaminonitrile was poor. For example, we obtained *N*-phenyl-β-aminocrotononitrile (**2g**) in an 87% yield when the reaction was carried out in the presence of an alcohol, whereas in the case of procedure C as described by Dedina et al. (16) the yield of **2g** was reported to be only 37%.

Lack of a general approach, consistency in yields, and inadequacies of *N*-substituent variants leave significant room for improvement in the methodology for preparation of secondary enaminonitriles notwithstanding the extensive work done by Dedina et al. (16). Herein, we report a very simple,

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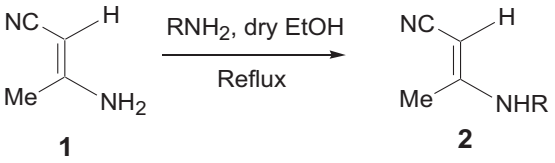
Table 1. Data for prepared compounds **2a**–**2p**.

Compound	R	Yield (%)[a]	mp (°C) or bp (°C)	$[\alpha]^{25}_{D}$ (°) (*c* 0.5 in $CHCl_3$)
2a	Me	65	54 to 55 (lit. value (16) mp 54 to 55)	—
2b	CH_2Me	70	45 (lit. value (16) mp 45 to 46)	—
2c	CH_2CH_2OH	76	70 to 71	—
2d	C_6H_{11}	97	88 to 89 (lit. value (16) mp 88 to 89)	—
2e	CH_2CO_2Et	72	44 to 45	—
2f	CH_2Ph	84	81 to 82 (lit. value (16) mp 78 to 79)	—
2g	Ph	87	116 (lit. value (16) mp 116 to 117)	—
2h	*p*-MeO·C_6H_4	80	126 to 127	—
2i	*o*-Me·C_6H_4	70	65 to 66	—
2j	*p*-Me·C_6H_4	81	90 to 91	—
2k	CH(Me)Ph	95	65 to 66	+100
2l	$CH(Me)CO_2Me$	74	150–153 (0.05 mm)	–52
2m	$CH(CHMe_2)CO_2Me$	82	160–167 (0.05 mm)	–96.83
2n	$CH(CH_2CHMe_2)CO_2Me$	71	170–175 (0.05 mm)	–95.6
2o	$CH(CH_2Ph)CO_2Me$	77	220–225 (0.01 mm)	+107.42
2p	$CHCH_2$(*p*-HO·C_6H_4) CO_2Me	70	195–200 (0.01 mm)	+119.11

[a]Yields of isolated products.

Scheme 1.



1 2

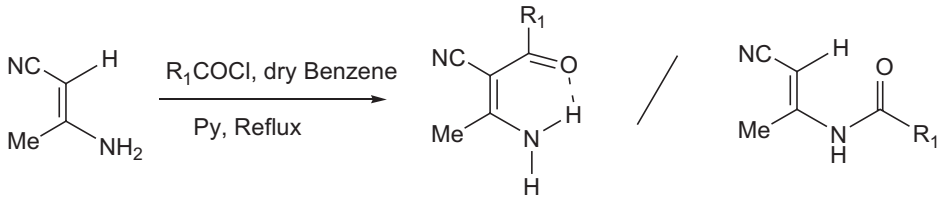
direct, and highly efficient general method for the one-pot preparation of secondary enaminonitriles **2a**–**2j** including the optically active ones **2k**–**2p** by reacting **1** with amines in refluxing dry ethyl alcohol (Scheme 1, Table 1). For the preparation of *N*-methyl-β-aminocrotononitrile (**2a**) and *N*-ethyl-β-aminocrotononitrile (**2b**), methyl ammonium chloride and ethyl ammonium chloride, respectively, were used in the presence of triethyl amine.

In the case of the optically active enaminonitriles **2k**–**2p**, the amino acids were first converted to their corresponding methyl ester hydrochlorides by treatment with thionyl chloride in refluxing dry methyl alcohol (18, 19). These ester hydrochlorides were then reacted with **1** in the presence of triethyl amine in refluxing ethyl alcohol. The amino acids used were (*S*)-(+)-alanine, (*S*)-(+)-leucine, (*S*)-(+)-valine, (*R*)-(+)-α-methylbenzyl amine, (*S*)-(–)-phenylalanine, and (*S*)-(–)-tyrosine. The homogeneity of the liquid products was checked by HPLC using a C-18 Bonda-pak column and a methanol–water (1:1) mixture as the mobile phase. The structures of these enaminonitriles are supported by consistent elemental and spectral analyses. Careful analysis of the ^{1}H NMR spectra of the isolated products is suggestive of the E conformation for the enaminonitriles (16). When compared with documented literature methods, the present procedure scores favorably in terms of simplicity, yields, choice of *N*-substituent variants, and purity of the products.

In our earlier investigations (5) on acylation of **1** we demonstrated that by choosing a suitable acid chloride it is possible to control the site of acylation to a large degree. β-Acylcyanoenaminonitriles thus obtained were easily converted to novel 5-substituted 1,2-azoles (8, 9). Although a high degree of success was achieved in terminal selection, there were examples where either a mixture of regioisomers or only *N*-acylated products were obtained. Since β-enaminones have proven to be valuable intermediates in the synthesis of a wide variety of heterocyclic compounds (20), we have initiated this study on the acylation reaction of secondary enaminonitriles to observe if there was any change in their preference for terminal selection when compared to primary enaminonitriles. Results obtained thus far indicate that *N*-substituted β-aminocrotononitriles show a strong preference for C-terminal selection when compared with the results obtained earlier for **1** (Scheme 2). Thus, *N*-benzyl-β-aminocrotononitrile (**2f**) on reaction with acid chlorides of benzoic acid, *o*-nitrobenzoic acid, *m*-nitrobenzoic acid, and thiophene-2-carboxylic acid afforded only *C*-acylated products in contrast to our earlier results with **1** whereby a mixture of regioisomers **3** and **4** (1:1) was obtained. The presence of compounds **3** and **4** in the reaction mixture was confirmed by ^{1}H NMR spectral analysis, and the pure regioisomers were obtained by column chromatography. A dramatic reversal of preference for site selection occurred when acylation of **2f** was carried out with isobutyryl chloride resulting in exclusive C-terminal selection. In an earlier experiment, treatment of **1** with isobutyryl chloride afforded only the *N*-acylated product, thereby precluding its use for the preparation of pyrazole (Scheme 2, Table 2). Such a strong preference by **2f** for C-terminal selection allowed us to synthesize pyrazoles that previously needed either separation of regioisomers or where the total lack of preference for C-terminal selection excluded their formation (Scheme 3, Table 3). Presently, we are working on the synthetic application of other secondary enaminonitriles including chiral ones.

Thus, easy access to secondary enaminonitriles provides a direct route for the synthesis of heterocycles that otherwise are not directly obtainable from acylation reactions of primary enaminonitriles. In addition, the availability of optically active secondary enaminonitriles is likely to provide

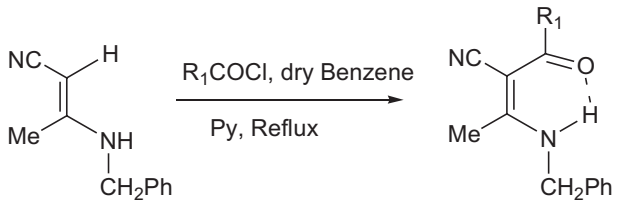
Scheme 2.



1 **3** **4**

R_1 = Ph, *o*-NO_2-C_6H_4, *m*-NO_2-C_6H_4, 2-thienyl, the product is a mixture (1:1) of **3** and **4**

R_1 = isobutyryl, the product is only **4**



2f **3a-3e**

R_1 = Ph, *o*-NO_2-C_6H_4, *m*-NO_2-C_6H_4, 2-thienyl, isobutyryl

Table 2. Data for the acylation reaction of *N*-benzyl-β-aminocrotononitrile (**2f**) and prepared compounds **3a**–**3e**.

Compound	R	R_1	mp (°C)	Yield (%)[a]
3a	CH_2Ph	Ph	84 to 85	71
3b	CH_2Ph	*o*-NO_2-C_6H_4	137 to 138	67
3c	CH_2Ph	*m*-NO_2-C_6H_4	123 to 124	70
3d	CH_2Ph	2-Thienyl	80 to 81	76
3e	CH_2Ph	Isobutyryl	88 to 89	80

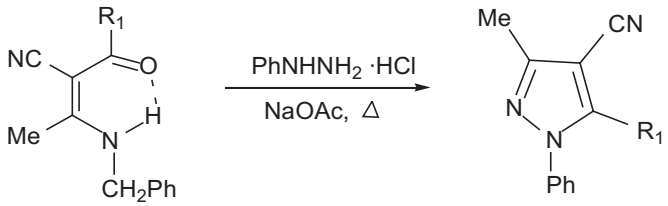
[a]Yields of isolated products.

opportunities for their utilization as chiral auxiliaries towards the synthesis of chiral heterocycles.

Experimental

Melting points were determined in open capillaries. NMR spectra were recorded using a Brucker AC-300 and (or) Brucker Avance 400 MHz spectrometer. Elemental analyses were performed using a PerkinElmer 240C elemental analyzer, mass spectra were obtained with an Hitachi RMU 6L and JMS-Ax505H mass spectrometer, and GC–MS spectra were obtained using an Agilnet 6890N. Optical rotations were measured on a Jasco Dip 360 digital polarimeter. HPLC was carried out using a Water Corporation UV detector and version 2.1 Mellenium software. UV and IR spectra were obtained using Hitachi U-2000 and Hitachi 270–30 spectrometers, respectively.

Scheme 3.



3a-3e **5a-5e**

Table 3. Data for prepared compounds **5a**–**5e**.

Compound	R_1	mp (°C)	Yield (%)[a]
5a	Ph	191 to 192	78
5b	*o*-NO_2-C_6H_4	155 to 156	67
5c	*m*-NO_2-C_6H_4	162 to 163	90
5d	2-Thienyl	204–206	67
5e	Isobutyryl	73 to 74	70

[a]Yields of isolated products.

β-Aminocrotononitrile and acid chlorides were prepared according to literature procedures in refs. 21 and 22, respectively.

General procedure

Preparation of N-substituted β-aminocrotononitriles

(*a*) A mixture of **1** (10 mmol), primary amine (10 mmol), and dry ethyl alcohol (40 mL) was refluxed for 2–5 h under dry conditions. Excess alcohol was distilled off

under reduced pressure, water was poured into the flask, and the contents were extracted with a suitable organic solvent. The organic layer was first washed with 2 N HCl, then with brine until neutral, it was then dried over anhydr. Na_2SO_4 and evaporated to dryness. Recrystallization of the crude product from a suitable solvent furnished the pure compound.

(*b*) A mixture of chiral amine (5 mmol), thionyl chloride (10 mmol), and dry methanol (15 mL) was refluxed for 2.5 h. Excess methanol and thionyl chloride were removed under reduced pressure and the residue was dried under vacuum. A solution of **1** (5 mmol) in dry ethyl alcohol (20 mL) was added to the residue with stirring at 0 °C followed by addition of triethylamine (5 mmol) in dry ethyl alcohol (5 mL). The reaction mixture was refluxed for 3 h. Following the usual work-up, purification of the crude product by column chromatography on silica gel (100–200 mesh) with 30% ethyl acetate – hexane as eluent afforded the product as a thick liquid.

Acylation reaction of *N*-benzyl-β-aminocrotononitrile with acid chlorides

The acid chloride (5 mmol) in dry benzene (10 mL) was added dropwise under ice cold conditions to a magnetically stirred solution of **2f** (5 mmol) in dry benzene (50 mL) and pyridine (15 mmol). Upon completion of the addition, stirring was continued for an additional 1 h at room temperature, and then refluxed for 3–5 h. The reaction mixture was then poured on ice water, acidified with HCl (2 N) followed by extraction with ethyl acetate (3 × 25 mL). The organic layer was then washed with a 5% $NaHCO_3$ solution followed by brine and then dried over anhydr. Na_2SO_4. Removal of the solvent afforded solid materials, which on crystallization furnished pure acylated products.

Preparation of pyrazoles

A mixture of α-cyanoenaminone (3 mmol) and phenyl hydrazine reagent (23) (9 mmol) was heated on a steam bath for 20–45 min, during which a yellow oily material separated. The reaction mixture was acidified with acetic acid (50%) followed by neutralization with solid $NaHCO_3$. It was then extracted with diethyl ether or ethyl acetate (3 × 20 mL). The organic layer was washed with brine and dried over anhydr. Na_2SO_4. The crude material obtained on removal of the solvent was purified by crystallization from a suitable solvent or by column chromatography (silica gel, 60–120 mesh, 5% ethyl acetate – petroleum ether).

Spectral data of prepared compounds 2a–2p

2a

UV (λ_{max}, EtOH, nm): 260 ($\epsilon = 1.97 \times 10^4$). IR (KBr, cm^{-1}): 3336, 2925, 2188, 1603, 1545. ^{1}H NMR ($CDCl_3$, ppm) δ: 2.12 (3H, s, =C-C*H*$_3$), 2.72 (3H, d, *J* = 5.9 Hz, NHC*H*$_3$), 3.75 (1H, s, =C*H*CN), 5.21 (1H, bs, -N*H*). MS *m*/*z*: 96 (M^+). Anal. calcd. for $C_5H_8N_2$ (%): C 62.47, H 8.39, N 29.14; found: C 62.50, H 8.36, N 29.19.

2b

UV (λ_{max}, EtOH, nm): 259 ($\epsilon = 2.08 \times 10^4$). IR (KBr, cm^{-1}): 3329, 2188, 1601, 1544, 1458. ^{1}H NMR ($CDCl_3$, ppm) δ: 1.16 (3H, t, *J* = 7.18 Hz, -CH_2CH_3), 2.04 (3H, s, C*H*$_3$), 2.93 (2H, m, C*H*$_2$CH$_3$), 3.69 (1H, s, =C*H*CN), 4.55 (1H, bs, -N*H*). ^{13}C NMR ($CDCl_3$, ppm) δ: 13.17, 19.79, 38.37, 58.69, 122.53, 160.39. MS *m*/*z*: 110 (M^+). Anal. calcd. for $C_6H_{10}N_2$ (%): C 65.42, H 9.15, N 25.43; found: C 65.46, H 9.12, N 25.47.

2c

UV (λ_{max}, EtOH, nm): 259 ($\epsilon = 1.93 \times 10^4$). IR (KBr, cm^{-1}): 3389, 2927, 2196, 1600, 1451. ^{1}H NMR ($CDCl_3$, ppm) δ: 2.01 (3H, s, -C*H*$_3$), 2.94 (2H, q, *J* = 5.6 Hz, -NHC*H*$_2$-), 3.49 (2H, q, *J* = 5.6 Hz, -C*H*$_2$OH), 3.78 (1H, s, =C*H*CN), 4.73 (1H, t, *J* = 5.6 Hz, -CH_2O*H*), 6.88 (1H, bs, -N*H*). ^{13}C NMR ($CDCl_3$, ppm) δ: 19.67, 45.90, 57.56, 58.77, 122.93, 161.18. MS *m*/*z*: 126 (M^+). Anal. calcd. for $C_6H_{10}N_2O$ (%): C 57.12, H 7.99, N 22.21; found: C 57.15, H 7.94, N 22.25.

2d

UV (λ_{max}, EtOH, nm): 263 ($\epsilon = 1.95 \times 10^4$). IR (KBr, cm^{-1}): 3307, 3073, 2931, 2855, 2185, 1595, 1548, 1446. ^{1}H NMR ($CDCl_3$, ppm) δ: 1.13–1.94 (10H, com, H atoms of cyclohexane ring), 2.08 (3H, s, =CC*H*$_3$), 3.05 (1H, tq, *J* = 4, 9 Hz, proton of cyclohexane ring α to NH), 3.79 (1H, s, =C*H*CN), 4.33 (1H, bs, -N*H*). ^{13}C NMR ($CDCl_3$, ppm) δ: 20.59, 24.54, 25.19, 32.05, 34.28, 51.72, 52.09, 59.65, 122.34, 158.67. MS *m*/*z*: 164 (M^+). Anal. calcd. for $C_{10}H_{16}N_2$ (%): C 73.12, H 9.82, N 17.06; found: C 73.17, H 9.78, N 17.10.

2e

UV (λ_{max}, EtOH, nm): 255 ($\epsilon = 2.00 \times 10^4$). IR (KBr, cm^{-1}): 3399, 3377, 3056, 2995, 2912, 2189, 1731, 1600, 1526, 1474, 1408. ^{1}H NMR ($CDCl_3$, ppm) δ: 1.09 (3H, t, *J* = 7.1 Hz, -CH_2CH_3), 1.96 (3H, s, =CC*H*$_3$), 3.53 (1H, s, =C*H*CN), 3.57 (2H, d, *J* = 5.1 Hz, -NHC*H*$_2$-), 4.05 (2H, q, -C*H*$_2$CH$_3$), 5.42 (1H, bs, -N*H*). ^{13}C NMR ($CDCl_3$, ppm) δ: 13.53, 19.14, 44.24, 60.73, 61.20, 120.92, 159.64, 168.59. MS *m*/*z*: 168 (M^+). Anal. calcd. for $C_8H_{12}N_2O_2$ (%): C 57.12, H 7.19, N 16.65; found: C 57.15, H 7.25, N 16.63.

2f

UV (λ_{max}, EtOH, nm): 272 ($\epsilon = 2.30 \times 10^4$). IR (KBr, cm^{-1}): 3304, 3088, 2192, 1594, 1560, 1492, 1446. ^{1}H NMR ($CDCl_3$, ppm) δ: 2.13 (3H, s, -C*H*$_3$), 3.86 (1H, s, =C*H*CN), 4.13 (2H, d, *J* = 5.02 Hz, -C*H*$_2$Ph), 4.64 (1H, bs, -N*H*), 7.25–7.38 (5H, m, Ar-*H*). ^{13}C NMR ($CDCl_3$, ppm) δ: 20.12, 47.46, 60.83, 121.71, 127.56, 127.90, 129.32, 136.40, 159.87. MS *m*/*z*: 172 (M^+). Anal. calcd. for $C_{11}H_{12}N_2$ (%): C 76.71, H 7.02, N 16.27; found: C 76.75, H 6.97, N 16.30.

2g

UV (λ_{max}, EtOH, nm): 288 ($\epsilon = 1.61 \times 10^4$). IR (KBr, cm^{-1}): 3266, 3125, 3058, 2199, 1612, 1586, 1542. ^{1}H NMR ($CDCl_3$, ppm) δ: 2.24 (3H, s, =CC*H*$_3$), 4.40 (1H, s, =C*H*CN), 6.13 (1H, bs, -N*H*), 7.12–7.38 (5H, m, Ar-H). ^{13}C NMR ($CDCl_3$, ppm) δ: 20.50, 64.88, 121.26, 123.85, 125.67, 129.51, 138.46, 158.29. MS *m*/*z*: 158 (M^+). Anal. calcd. for $C_{10}H_{10}N_2$ (%): C 75.92, H 6.37, N 17.71; found: C 75.96, H 6.42, N 17.67.

2h

UV (λ_{max}, EtOH, nm): 284 ($\epsilon = 1.61 \times 10^4$). IR (KBr, cm^{-1}): 3304, 3278, 2191, 1605, 1514. ^{1}H NMR ($CDCl_3$, ppm) δ: 2.22 (3H, s, =CC*H*$_3$), 3.80 (3H, s, -OC*H*$_3$), 4.12 (1H, s,

=C*H*CN), 5.94 (1H, bs, -N*H*), 6.88 and 7.06 (each 2H, d, *J* = 8.2 Hz, Ar-*H*). ^{13}C NMR ($CDCl_3$, ppm) δ: 20.21, 55.44, 63.73, 82.14, 114.32, 121.58, 126.52, 131.0, 157.81, 159.54. MS *m*/*z*: 188 (M^+). Anal. calcd. for $C_{11}H_{12}N_2O$ (%): C 70.19, H 6.43, N 14.88; found: C 70.24, H 6.39, N 14.91.

2i

UV (λ_{max}, EtOH, nm): 293 ($\epsilon = 1.93 \times 10^4$). IR (KBr, cm^{-1}): 3276, 2190, 1580, 1521, 1438. ^{1}H NMR ($CDCl_3$, ppm) δ: 2.20 (3H, s, =CC*H*$_3$), 2.24 (3H, s, -*o*-C*H*$_3$ C_6H_4), 3.81 (1H, s, =C*H*CN), 5.82 (1H, bs, -N*H*), 7.10–7.23 (4H, m, Ar-*H*). ^{13}C NMR ($CDCl_3$, ppm) δ: 17.18, 19.75, 63.89, 119.00, 126.41, 126.55, 126.67, 126.80, 126.97, 130.99, 159.90. MS *m*/*z*: 172 (M^+). Anal. calcd. for $C_{11}H_{12}N_2$ (%): C 76.75, H 7.02, N 16.27; found: C 76.79, H 6.93, N 16.21.

2j

UV (λ_{max}, EtOH, nm): 294 ($\epsilon = 1.94 \times 10^4$). IR (KBr, cm^{-1}): 3312, 2184, 1598, 1548, 1310. ^{1}H NMR ($CDCl_3$, ppm) δ: 2.21 (3H, s, =CC*H*$_3$), 2.32 (3H, s, *p*-C*H*$_3$ C_6H_4), 4.28 (1H, s, =C*H*CN), 5.96 (1H, bs, -N*H*), 6.99 and 7.14 (each 2H, d, *J* = 8.2 Hz, Ar-*H*). MS *m*/*z*: 172 (M^+, 100). Anal. calcd. for $C_{11}H_{12}N_2$ (%): C 76.75, H 7.02, N 16.27; found: C 76.81, H 7.09, N 16.32.

2k

UV (λ_{max}, EtOH, nm): 258 ($\epsilon = 2.10 \times 10^4$). IR (KBr, cm^{-1}): 3301, 3061, 2190, 1596, 1545, 1446, 1382. ^{1}H NMR ($CDCl_3$, ppm) δ: 1.45 (3H, d, *J* = 6.7 Hz, -CHC*H*$_3$), 2.11 (3H, s, -C*H*$_3$), 3.61 (1H, s, =C*H*CN), 4.28 (1H, m, *J* = 6.71 Hz, -C*H*-CH$_3$), 4.73 (1H, bs, -N*H*), 7.18–7.34 (5H, m, Ar-H). ^{13}C NMR ($CDCl_3$, ppm) δ: 20.54, 23.94, 53.61, 63.08, 121.79, 125.49, 125.67, 129.06, 142.61, 158.80. MS *m*/*z*: 186 (M^+). Anal. calcd. for $C_{12}H_{14}N_2$ (%): C 77.38, H 7.57, N 15.05; found: C 77.42, H 7.46, N 15.09.

2l

UV (λ_{max}, $CHCl_3$, nm): 257 ($\epsilon = 1.60 \times 10^4$). IR (as oil, cm^{-1}): 3322, 3076, 2956, 2850, 2199, 1740, 1607, 1546, 1454. ^{1}H NMR ($CDCl_3$, ppm) δ: 1.43 (3H, d, *J* = 6.9 Hz, -CHC*H*$_3$), 2.13 (3H, s, =CC*H*$_3$), 3.77 (1H, s, =C*H*CN), 3.78 (3H, s, -CO$_2$C*H*$_3$), 3.92 (1H, quintet, *J* = 7 Hz, -C*H*CO$_2$CH$_3$), 4.90 (1H, bs, -N*H*). ^{13}C NMR ($CDCl_3$, ppm) δ: 18.04, 20.78, 51.79, 53.14, 62.87, 121.36, 159.00, 173.33. MS *m*/*z*: 168 (M^+). Anal. calcd. for $C_8H_{12}N_2O_2$ (%): C 57.12, H 7.19, N 16.65; found: C 56.97, H 7.13, N 16.51.

2m

UV (λ_{max}, $CHCl_3$, nm): 256 ($\epsilon = 1.65 \times 10^4$). IR (as oil, cm^{-1}): 3332, 3074, 2966, 2877, 2197, 1738, 1604, 1541, 1436. ^{1}H NMR ($CDCl_3$, ppm) δ: 0.94 (3H, d, *J* = 6.75 Hz, -C*H*$_3$), 1.0 (3H, d, *J* = 6.75 Hz, -C*H*$_3$), 2.08–2.13 (1H, com, C*H*Me$_2$), 2.15 (3H, s, =CC*H*$_3$), 3.64 (1H, q, *J* = 5.8 Hz, -C*H*COOCH$_3$), 3.76 (3H, s, -CO$_2$C*H*$_3$), 3.81 (1H, s, =C*H*CN), 4.86 (1H, d, *J* = 7.2 Hz, -N*H*). ^{13}C NMR ($CDCl_3$, ppm) δ: 17.81, 18.60, 30.83, 31.75, 52.21, 61.36, 63.12, 120.99, 159.42, 171.85. MS *m*/*z*: 196 (M^+). Anal. calcd. for $C_{10}H_{16}N_2O_2$ (%): C 61.20, H 8.22, N 14.27; found: C 61.24, H 8.29, N 14.22.

2n

UV (λ_{max}, $CHCl_3$, nm): 256 ($\epsilon = 1.68 \times 10^4$). IR (as oil, cm^{-1}): 3319, 3074, 2957, 2871, 2198, 1739, 1604, 1543, 1437. ^{1}H NMR ($CDCl_3$, ppm) δ: 0.83 (3H, d, *J* = 6.2 Hz, -CHC*H*$_3$), 0.87 (3H, d, *J* = 6.2 Hz, -CHC*H*$_3$), 1.53–1.63 (3H, com, -C*H*$_2$-C*H*Me$_2$), 2.04 (3H, s, =CC*H*$_3$), 3.66 (3H, s, -CO$_2$C*H*$_3$), 3.71 (1H, s, =C*H*CN), 3.75 (1H, q, *J* = 7.3 Hz, -CHCO$_2$C*H*$_3$), 5.12 (1H, d, *J* = 7.6 Hz, -N*H*). ^{13}C NMR ($CDCl_3$, ppm) δ: 19.75, 21.75, 22.22, 24.54, 41.65, 52.82, 54.95, 62.07, 120.92, 159.69, 172.81. MS *m*/*z*: 210 (M^+). Anal. calcd. for $C_{11}H_{18}N_2O_2$ (%): C 62.83, H 8.63, N 13.32; found: C 62.90, H 8.70, N 13.38.

2o

UV (λ_{max}, $CHCl_3$, nm): 258 ($\epsilon = 2.41 \times 10^4$). IR (as oil, cm^{-1}): 3318, 3029, 3066, 2953, 2198, 1740, 1604, 1541, 1438. ^{1}H NMR ($CDCl_3$, ppm) δ: 2.09 (3H, s, =CC*H*$_3$), 3.03 (1H, dd, *J* = 5.76, 13.57 Hz, -C*H*$_2$Ph), 3.73 (3H, s, -CO$_2$CH$_3$), 3.84 (1H, s, =C*H*CN), 4.16 (1H, dt, *J* = 5.76, 6.33 Hz, -C*H*CH$_2$-), 4.77 (1H, bd, *J* = 6.33 Hz, -N*H*), 7.05–7.33 (5H, m, Ar-*H*). ^{13}C NMR ($CDCl_3$, ppm) δ: 20.03, 36.80, 52.50, 56.30, 61.80, 63.00, 120.70, 127.40, 128.60, 129.00, 134.90, 158.30, 171.30. MS *m*/*z*: 245 (MH^+). Anal. calcd. for $C_{14}H_{16}N_2O_2$ (%): C 68.83, H 6.60, N 11.46; found: C 68.93, H 6.65, N 11.41.

2p

UV (λ_{max}, $CHCl_3$, nm): 258 ($\epsilon = 1.81 \times 10^4$). IR (as oil, cm^{-1}): 3318, 3074, 2976, 2871, 2199, 1739, 1604, 1516, 1442. ^{1}H NMR ($CDCl_3$, ppm) δ: 2.09 (3H, s, =CC*H*$_3$), 2.96 (1H, dd, *J* = 5.5, 13.8 Hz, -C*H*$_2$), 3.08 (1H, dd, *J* = 5.8, 13.8 Hz, -C*H*$_2$), 3.74 (3H, s, -CO$_2$C*H*$_3$), 3.83 (1H, s, =C*H*CN), 4.07–4.15 (1H, com, -C*H*-), 4.78 (1H, bd, *J* = 6.8 Hz, -N*H*), 5.98 (1H, bs, -O*H*), 6.77 and 6.92 (each 2H, d, *J* = 8.3 Hz, Ar-*H*). ^{13}C NMR ($CDCl_3$, ppm) δ: 20.28, 36.14, 52.65, 56.76, 62.07, 111.65, 121.23, 126.36, 130.25, 145.15, 155.60, 159.34, 171.78. MS *m*/*z*: 260 (M^+). Anal. calcd. for $C_{14}H_{16}N_2O_3$ (%): C 64.60, H 6.19, N 10.76; found: C 64.72, H 6.26, N 10.71.

Spectral data of prepared compounds 3a–3e

3a

UV (λ_{max}, EtOH, nm): 321 ($\epsilon = 1.85 \times 10^4$). IR (KBr, cm^{-1}): 2198, 1608, 1465, 1321. ^{1}H NMR ($CDCl_3$, ppm) δ: 2.40 (3H, s, C*H*$_3$), 4.62 (2H, d, *J* = 5.9 Hz, C*H*$_2$Ph), 7.21–7.79 (10H, m, Ar-*H*), 12.66 (1H, bs, N*H*). ^{13}C NMR ($CDCl_3$, ppm) δ: 18.1, 48.2, 82.5, 121.3, 127.0, 127.7, 128.0, 128.3, 129.2, 131.2, 135.2, 139.1, 172.1, 192.6. MS *m*/*z*: 276 (M^+). Anal. calcd. for $C_{18}H_{16}N_2O$ (%): C 78.24, H 5.84, N 10.14; found: C 78.29, H 5.81, N 10.16.

3b

UV (λ_{max}, EtOH, nm): 310 ($\epsilon = 1.63 \times 10^4$). IR (KBr, cm^{-1}): 2199, 1605, 1584, 1473, 1316. ^{1}H NMR ($CDCl_3$, ppm) δ: 2.39 (3H, s, C*H*$_3$), 4.64 (2H, d, *J* = 6.2 Hz, C*H*$_2$Ph), 7.0–8.22 (9H, m, Ar-*H*), 11.97 (1H, bs, N*H*). ^{13}C NMR ($CDCl_3$, ppm) δ: 18.5, 48.6, 84.1, 120.0, 124.8, 127.3, 128.7, 128.8, 129.6, 130.6, 134.3, 135.3, 136.2, 146.1, 171.9, 190.7. MS *m*/*z*: 321 (M^+). Anal. calcd. for $C_{18}H_{15}N_3O_3$ (%): C 67.28, H 4.71, N 13.08; found: C 67.33, H 4.69, N 13.11.

3c

UV (λ_{max}, EtOH, nm): 324 ($\epsilon = 2.08 \times 10^4$). IR (KBr, cm^{-1}): 2200, 1601, 1528, 1461, 1317. ^1H NMR ($CDCl_3$, ppm) δ: 2.43 (3H, s, C*H*$_3$), 4.67 (2H, d, *J* = 5.9 Hz, C*H*$_2$Ph), 7.28–7.42 (5H, m, CH$_2$*Ph*), 7.60 (1H, t, *J* = 7.9 Hz, 5-H of *m*-NO$_2$-Ph ring), 8.12 (1H, d, *J* = 7.8 Hz, 6-H of *m*-NO$_2$-Ph ring), 8.30 (1H, d, *J* = 7.8 Hz, 4-H of *m*-NO$_2$-Ph ring), 8.60 (1H, s, 2-H of *m*-NO$_2$-Ph ring), 12.57 (1H, bs, N*H*). ^{13}C NMR ($CDCl_3$, ppm) δ: 18.4, 48.6, 82.6, 120.7, 123.3, 125.7, 127.4, 128.7, 129.3, 129.5, 133.6, 134.9, 140.6, 148.1, 172.8, 189.6. MS *m*/*z*: 321 (M^+). Anal. calcd. for $C_{18}H_{15}N_3O_3$ (%): C 67.28, H 4.71, N 13.08; found: C 67.32, H 4.72, N 13.10.

3d

UV (λ_{max}, EtOH, nm): 340 ($\epsilon = 1.96 \times 10^4$), 249 ($\epsilon = 1.22 \times 10^4$). IR (KBr, cm^{-1}): 2195, 1619, 1601, 1544, 1511, 1453. ^1H NMR ($CDCl_3$, ppm) δ: 2.38 (3H, s, C*H*$_3$), 4.61 (2H, d, *J* = 5.8 Hz, C*H*$_2$Ph), 7.0–8.25 (8H, m, Ar-*H*), 12.45 (1H, bs, N*H*). MS *m*/*z*: 282 (M^+). Anal. calcd. for $C_{16}H_{14}N_2OS$ (%): C 68.07, H 4.99, N 9.92; found: C 68.09, H 4.96, N 9.95.

3e

UV (λ_{max}, EtOH, nm): 304 ($\epsilon = 1.58 \times 10^4$). IR (KBr, cm^{-1}): 2192, 1623, 1574, 1468. ^1H NMR ($CDCl_3$, ppm) δ: 1.07 (3H, d, *J* = 7.1 Hz, CH(C*H*$_3$)CH$_3$), 1.14 (3H, d, *J* = 7.1 Hz, CH(CH$_3$)C*H*$_3$), 2.30 (3H, s, C*H*$_3$), 3.14 (1H, m, C*H*(CH$_3$)$_2$), 4.54 (2H, d, *J* = 6.1 Hz, C*H*$_2$Ph), 7.34 (5H, m, Ar-*H*), 12.26 (1H, bs, N*H*). ^{13}C NMR ($CDCl_3$, ppm) δ: 18.0, 19.1, 31.0, 37.8, 48.2, 82.6, 121.0, 127.2, 128.4, 129.3, 135.5, 170.8, 203.3. MS *m*/*z*: 242 (M^+). Anal. calcd. for $C_{15}H_{18}N_2O$ (%): C 74.34, H 7.49, N 11.56; found: C 74.30, H 7.52, N 11.58.

Spectral data of prepared compounds 5a–5e

5a

UV (λ_{max}, EtOH, nm): 255 ($\epsilon = 1.14 \times 10^4$). IR (KBr, cm^{-1}): 2220, 1593, 1538, 1504, 1450, 1424, 1137. ^1H NMR ($CDCl_3$, ppm) δ: 2.50 (3H, s, C*H*$_3$), 7.24–7.52 (10H, m, Ar-*H*). MS *m*/*z*: 259 (M^+). Anal. calcd. for $C_{17}H_{13}N_3$ (%): C 78.74, H 5.05, N 16.20; found: C 78.79, H 5.02, N 16.23.

5b

UV (λ_{max}, EtOH, nm): 246 ($\epsilon = 1.39 \times 10^4$). IR (KBr, cm^{-1}): 2228, 1595, 1528, 1502, 1445. ^1H NMR ($CDCl_3$, ppm) δ: 2.54 (3H, s, C*H*$_3$), 7.0–8.06 (9H, m, Ar-*H*). MS *m*/*z*: 304 (M^+). Anal. calcd. for $C_{17}H_{12}N_4O_2$ (%): C 67.10, H 3.97, N 18.41; found: C 67.18, H 3.95, N 18.45.

5c

UV (λ_{max}, EtOH, nm): 254 ($\epsilon = 1.57 \times 10^4$). IR (KBr, cm^{-1}): 2227, 1596, 1526, 1501, 1429, 1387, 1348. ^1H NMR ($CDCl_3$, ppm) δ: 2.53 (3H, s, C*H*$_3$), 7.22–8.28 (9H, m, Ar-*H*). ^{13}C NMR ($CDCl_3$, ppm) δ: 12.54, 94.60, 113.4, 123.93, 124.55, 125.30, 128.78, 129.16, 129.53, 130.21, 134.64, 138.02, 145.02, 148.36, 152.95. MS *m*/*z*: 304 (M^+). Anal. calcd. for $C_{17}H_{12}N_4O_2$ (%): C 67.10, H 3.97, N 18.41; found: C 67.17, H 3.99, N 18.44.

5d

UV (λ_{max}, EtOH, nm): 237 ($\epsilon = 0.59 \times 10^4$), 249 ($\epsilon = 1.22 \times 10^4$). IR (KBr, cm^{-1}): 2221, 1593, 1545, 1513, 1456, 1416. ^1H NMR ($CDCl_3$, ppm) δ: 2.48 (3H, s, C*H*$_3$), 6.90–7.90 (8H, m, Ar-*H*). MS *m*/*z*: 265 (M^+). Anal. calcd. for $C_{15}H_{11}N_3S$ (%): C 67.91, H 4.18, N 15.84; found: C 67.95, H 4.20, N 15.88.

5e

UV (λ_{max}, EtOH, nm): 255 ($\epsilon = 1.51 \times 10^4$). IR (KBr, cm^{-1}): 2222, 1595, 1545, 1513, 1460. ^1H NMR ($CDCl_3$, ppm) δ: 1.38 (6H, d, *J* = 7.2 Hz, (C*H*$_3$)$_2$), 2.40 (3H, s, C*H*$_3$), 3.07 (1H, heptet, *J* = 7.2 Hz, C*H*(CH$_3$)$_2$), 7.32–7.52 (5H, m, Ar-*H*). ^{13}C NMR ($CDCl_3$, ppm) δ: 12.31, 18.94, 21.43, 89.85, 114.40, 126.09, 128.22, 129.15, 138.30, 152.62, 155.57. MS *m*/*z*: 225 (M^+). Anal. calcd. for $C_{14}H_{15}N_3$ (%): C 74.64, H 6.71, N 18.65; found: C 74.69, H 6.69, N 18.63.

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