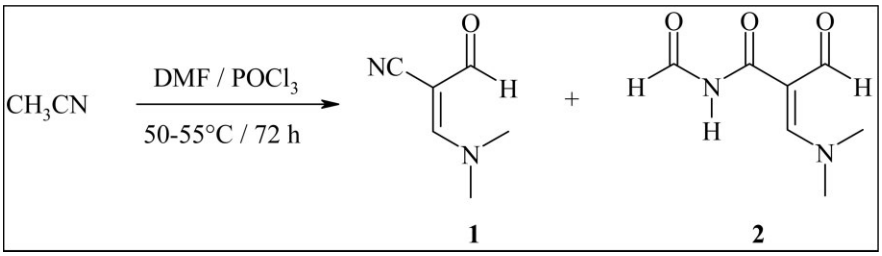
Vilsmeier–Haack Formylation of Acetonitrile Revisited: Synthesis of Novel Pyrazolo[1,5-*a*]pyrimidines and Triazolo[1,5-*a*]pyrimidine

Maruti G. Ghagare, Dilip R. Birari, Deepak P. Shelar, Raghunath B. Toche, and Madhukar N. Jachak*

Department of Chemistry, Organic Chemistry Research Center, K.T.H.M. College, Nashik 422002, Maharashtra, India
*E-mail: mn_jachak@hotmail.com

Received July 1, 2008
DOI 10.1002/jhet.76
Published online 13 April 2009 in Wiley InterScience (www.interscience.wiley.com).



Vilsmeier–Haack formylation of acetonitrile using dimethylformamide and phosphorus oxychloride leading to a novel intermediate, *N*-((*E*)-3-(dimethylamino)-2-formylacryloyl)formamidine **2** and its utility in the synthesis of pyrimidine-fused heterocycles such as pyrazolo[1,5-*a*]pyrimidines and triazolo[1,5-*a*]pyrimidine is reported.

J. Heterocyclic Chem., **46**, 327 (2009).

INTRODUCTION

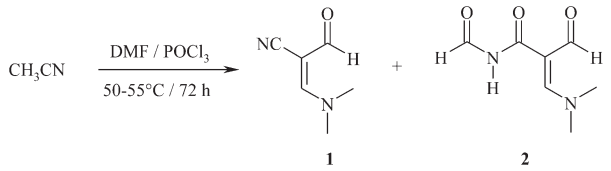
The synthesis of pyrazolo[1,5-*a*]pyrimidines is a promising avenue of research owing to various bioactivities displayed by this class of compounds. They have been established as selective inhibitors of adenosine cyclic mono phosphate (cAMP) phosphodiesterase *in vitro* [1,2]. In addition to this some of these compounds showed antischistosomal activity [3]. Another class of compounds, [1,2,4]triazolo[1,5-*a*]pyrimidine derivatives are promising inhibitors against trypanosomatid parasites [4], displaying inhibition percentages far higher than those reached with traditional drugs used against *T. cruzi* and *L. donovani*, such as ketoconazole [5], pentavalent antimonials [6], nitroimidazole, and itraconazole [7].

Vilsmeier–Haack formylation has emerged as a powerful tool for the formylation of various organic compounds. In 1970, Reichardt and Kermer [8] demonstrated the synthesis of 3-dimethylamino-2-formyl acrylonitrile **1** *via* the Vilsmeier–Haack formylation of acetonitrile. However, after intensive investigation of the same reaction we have achieved two products, *i.e.*, 3-dimethylamino-2-formyl acrylonitrile **1** and an unusual product *N*-((*E*)-3-(dimethylamino)-2-formylacryloyl)formamidine **2** (Scheme 1). From literature, it was noted that the related synthons have been used for the synthesis of pyrimidines and condensed pyrimidines [9–12]. Previously, we have used compound **1** for the synthesis of different annulated heterocycles [13,14]. Considering the synthetic utility of Compound **1** [15–17] and our interest in this area [18–20] prompted us to perform various condensation reactions of **2** with 5(3)amino heterocycles. We herein report the synthesis of an unexpected compound, *N*-((*E*)-3-(dimethylamino)-2-formylacryloyl) formamidine **2** and its utility in the synthesis of pyrimidine-fused heterocycles such as pyrazolo[1,5-*a*]pyrimidines and triazolo[1,5-*a*]pyrimidine.

RESULTS AND DISCUSSION

The Vilsmeier–Haack formylation of acetonitrile was carried out by Reichardt and Kermer by refluxing the reaction mixture of acetonitrile, DMF, and phosphorus oxychloride (1:0.6:0.6 mol) to furnish 3-dimethylamino-2-formyl acrylonitrile **1** in 10–12% yield. The same reaction carried out by us resulted in the formation of two products **1** and **2**. Encouraged by these results, we optimized the reaction conditions using different molar ratios of DMF and phosphorus oxychloride with respect to acetonitrile (Table 1). The ratio of molar equivalents played an important role in the formation of compounds **1** and **2**. Thus, the best results were obtained when a mixture of acetonitrile, DMF, and phosphorus oxychloride (1:3:3 mol) was heated to 50–55°C for 72 h. The reaction mixture was then poured into ice and neutralized with sodium hydrogencarbonate. The resultant

Scheme 1. Vilsmeier–Haack formylation of acetonitrile leading to a novel intermediate **2**.



1 **2**

suspension was extracted with dichloromethane. The organic layer was dried and concentrated under vacuum to give crude product, which was then recrystallized from ethanol to afford a pale yellow solid, *i.e*., compound **2** in 25% yield. The aqueous layer was concentrated under vacuum to a semisolid, which on recrystallization with ethanol furnished compound **1** in 20% yield. Compound **1** gave satisfactory spectral and physical data and was identical with that of reported earlier [8].

The structure of compound **2** was deduced from its ^{I}H and ^{13}C NMR spectra. The mass spectrum of **2** displayed the molecular ion (M^+) peak at 170 *m/z,* which is consistent with the molecular weight of **2**. The ^{1}H NMR spectrum of **2** showed singlet at δ 8.03 representing olefinic proton, doublet at δ 9.10 corresponding to aldehyde proton neighboring to —NH of amide. The singlet at δ 9.31 represented another aldehyde proton. The other signals appeared at δ 3.20 (s, 3H, NCH_3) and 3.40 (s, 3H, NCH_3). The —NH proton appeared at δ 11.43 as abroad singlet.

We observed that Vilsmeier–Haack formylation of acetonitrile with the optimized reaction conditions furnished two compounds with different yields. The structure of compound **2** was also supported by further nucleophilic substitution reaction with 5(3)-amino heterocycles. Thus condensation of compound **2** with 5(3)-amino pyrazoles **3a-c** furnished pyrazolo[1,5-*a*]pyrimidines **4a-c** in (Scheme 2, Table 2) 75–80% yield. During condensation of **2** with **3a-c** it was observed that the *N*-formyl group in **2** undergoes hydrolysis to amido function in **4a-c**. The condensation of **2** with pyrimidine-2-carboxamidine **5** furnished 2-(pyrimidine-2-yl)pyrimidine-5-carboxamide **6** (Scheme 3) in 80% yield. Similarly, 1,2,4 triazolo[1,5-*a*]pyrimidine-6-carboxamide **8** (Scheme 4) was synthesized in 82% yield from the reaction of 5(3)-amino[1,2,4]triazole **7** with **2**. The structure of the compounds **4**, **6**, and **8** were determined from spectroscopic data. Several attempts to cyclize **2** with 2-amino heterocycles **9a-e** did not lead to the desired product (**11a-e**). However, compound **2** on condensation with 2-aminopyridines or 2-aminopyrimidine in ethanol at reflux temperature furnished open chain compounds **10a-e** in 75–80% yield (Scheme 5, Table 3). It was interesting to observe that, the condensation of **2** with *o*-phenylenediamine **12** under similar reaction conditions furnished open chain compound **13** with the *N*-formyl group remaining intact (Scheme 6). Attempts to cyclize compound **12–14** were unsuccessful.

To conclude the Vilsmeier–Haack formylation of acetonitrile with optimized reaction conditions leads to a highly stable synthone *N*-((*E*)-3-(dimethylamino)-2-formyl acryloyl)formamide **2** which can further be used for the synthesis of various new heterocycles. Herein, we have reported the synthesis of some pyrazolopyrimidines and triazolopyrimidines. These heterocycles can exhibit a number of bioactivities specifically inhibitory action against cAMP phosphodiesterase. Biological investigations are in progress in our laboratory and shall be reported in a due course.

EXPERIMENTAL

Melting points were determined on a Buchi melting point apparatus, Mod. B-545 and are uncorrected. The ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on a Varian XL-300 spectrometer. Chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane, and multiplicities are given as s (singlet), d (doublet), t (triplet), q (quartet), or m (multiplate). The solvent for NMR spectra was DMSO-d_6 unless otherwise stated. Infrared spectra were taken on Thermo Electron Corporation NICOLET 380 FTIR

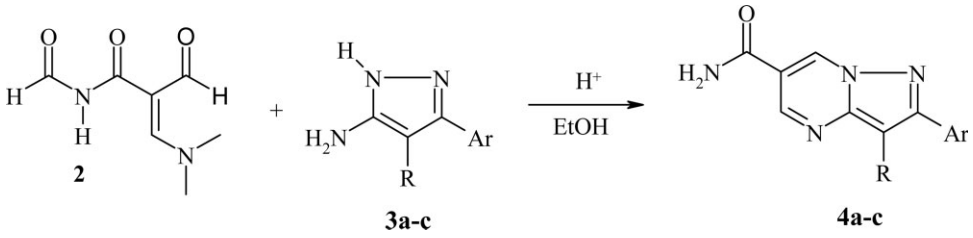
Table 1

Vilsmeier–Haack formylation of acetonitrile,[a] comparison of the product yield with the molar proportion.

Entry	CH_3CN (molar equiv.)	DMF (molar equiv.)	$POCl_3$ (molar equiv.)	Compound 1 Yield (%)[b]	Compound 2 Yield (%)[b]
1	1 mol	0.6 mol	0.6 mol	12.00%	02.50%
2	1 mol	1 mol	1 mol	11.50%	04.70%
3	1 mol	2 mol	2 mol	10.70%	11.90%
4	1 mol	1 mol	2 mol	04.00%	05.20%
5	1 mol	2 mol	1 mol	–	–
6	1 mol	3 mol	3 mol	20.00%	25.00%

[a] Carried out at 50–55°C for 72 h.
[b] Isolated yields.

Scheme 2. Synthesis of compound **4a-c**.



instrument in potassium bromide pellets unless otherwise stated. Mass spectrum was recorded on Shimadzu GC-MS QP 2010A mass spectrometer with an ionization potential of 70 eV. Elemental analysis was performed on a Hosli CH-Analyzer and was within ±0.4 of the theoretical percentage. All reactions were monitored by thin layer chromatography, carried out on 0.2-mm silica gel 60 F-254 (Merck) plates using UV light (254 and 366 nm) for detection. Common reagent grade chemicals are either commercially available and were used without further purification or prepared by standard literature procedures.

***N*-((E)-3-(Dimethylamino)-2-formylacryloyl) formamidine (2).** To a stirred solution of acetonitrile (41.05 g, 1000 mmol) and DMF (219.30 g, 3000 mmol) at 0–5°C was added dropwise over 1.5 h phosphorus oxychloride (459.99 g, 3000 mmol). The mixture was stirred at 50–55°C for 72 h. It was then quenched in ice, neutralized with sodium hydrogencarbonate. The resultant suspension was extracted with dichloromethane (9 × 500 mL). The combined organic extractions were washed with saturated aqueous NaCl and dried. The solvent was evaporated under reduced pressure, and the solid residue was recrystallized from ethanol affording compound 2 as a pale yellow solid, 42.5 g (25%) (Table 1, Entry 6); m.p 145–147°C, IR (KBr): 3049, 2920, 1700, 1653, 1578, 1273, 1176, 840 cm^{-1}. ^1H NMR (300 MHz, DMSO): δ 11.43 (d, J = 6.9 Hz,1H, NH), 9.31 (s, 1H, CHO), 9.10 (d, J = 9.9 Hz,1H, NH—CHO), 8.03 (s, 1H, CH), 3.41 (s, 3H, N—CH_3), 3.21 (s, 3H, N—CH_3). ^{13}C NMR (75 MHz, DMSO): δ 186.8, 164.3, 163.5, 162.7, 101.7, 48.6, 43.3. *Anal*. Calcd. for $C_7H_{10}N_2O_3$ Calcd. C: 49.41; H: 5.92; N: 16.46. Found. C: 49.39; H: 5.90; N: 16.47.

General procedure for the synthesis of compound 4a-c, 6, 8, 10a-e and 13

2-(4-Bromo-phenyl)-pyrazolo[1,5-a]pyrimidine-6-carboxalic acid amide (4a). A mixture of 2 (0.5 g, 2.9 mmol), 3a (0.88 g, 3.7 mmol) in ethanol (2.5 mL) and catalytic amount of acetic acid was refluxed until the starting material had been consumed in the reaction (4–5 h, TLC monitoring). Reaction mass was then cooled to room temperature. The precipitated solid was collected by filtration and washed with cold ethanol to obtain the crude product which was then recrystallized from ethanol to give compound 4a as brown solid, 0.745 g (80%); mp 318–320°C. IR (KBr): 3371, 3179, 3033, 1651, 1614, 1452, 1396, 77 cm^{-1}. ^1H NMR (300 MHz, DMSO): δ 9.53 (d, J = 3.0 Hz, 1H, Ar-H), 8.91 (d, J = 3.0 Hz, 1H, Ar-H), 8.18 (bs, 1H, NH), 8.03 (d, J = 8.4 Hz, 2H, Ar-H), 7.74 (bs, 1H, NH), 7.70 (d, J = 8.70 Hz, 2H, Ar-H), 7.38 (s, 1H, Ar-H). ^{13}C NMR (75 MHz, DMSO): δ 163.7, 157.9, 148.6, 146.7, 134.9, 132.6, 132.1, 128.9, 127.3, 126.6, 124.2, 121.9, 85.5. *Anal*. Calcd. for $C_{13}H_9BrN_4O$ Calcd. C: 49.23; H: 2.86; N: 17.67. Found. C: 49.25; H: 2.80; N: 17.50.

(4-Chloro-phenyl)-pyrazolo[1,5-a]pyrimidine-6-carboxalic acid amide (4b). Brown solid; Yield: 75%; mp 308–310°C. IR (KBr): 3373, 3178, 3035, 1651, 1614, 1453, 1396, 1614, 1097 cm^{-1}. ^1H NMR (300 MHz, DMSO): δ 9.52 (d, J = 1.5 Hz, 1H, Ar-H), 8.90 (d, J = 1.8 Hz, 1H, Ar-H), 8.18 (bs, 1H, NH), 8.08 (d, J = 8.7 Hz, 2H, Ar-H), 7.73 (bs, 1H, NH), 7.57 (d, J = 8.4 Hz, 2H, Ar-H), 7.36 (s, 1H, Ar-H). ^{13}C NMR (75 MHz, DMSO): δ 163.1, 157.6, 148.4, 146.0, 135.4, 132.4, 131.6, 128.6, 126.7, 126.1, 124.7, 122.1, 84.5. *Anal*. Calcd. for $C_{13}H_9ClN_4O$ Calcd. C: 57.26; H: 3.33; N: 20.55. Found. C: 57.20; H: 3.25; N: 20.50.

3-Cyano-pyrazolo[1,5-a]pyrimidine-6-carboxalic acid amide (4c). Yellow solid; Yield: 78%; mp 310–312°C. IR (KBr): 3395, 3328, 3058, 3121, 2235, 1674, 1624, 1421 cm^{-1}. ^1H NMR (300 MHz, DMSO): δ 9.74 (d, J = 2.1 Hz, 1H, Ar-H), 9.20 (d, J = 2.1 Hz, 1H, Ar-H), 8.94 (s, 1H, Ar-H), 8.33 (bs, 1H, NH), 7.93 (bs, 1H, NH). ^{13}C NMR (75 MHz, DMSO): δ 162.9, 152.8, 149.7, 149.0, 137.5, 117.9, 112.6, 81.5. *Anal*. Calcd. for $C_8H_5N_5O$ Calcd. C: 51.34; H: 2.69; N: 37.42. Found. C: 51.20; H: 2.55; N: 37.40.

2-(Pyrimidine-2-yl)pyrimidine-5-carboxamide (6). White solid; Yield: 80%; mp 315–317°C. IR (KBr): 3353, 3156, 3057,

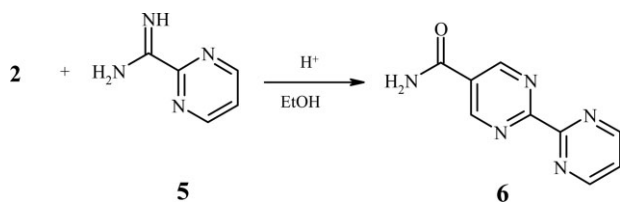
Table 2

Synthesis of compounds **4a-c**[a].

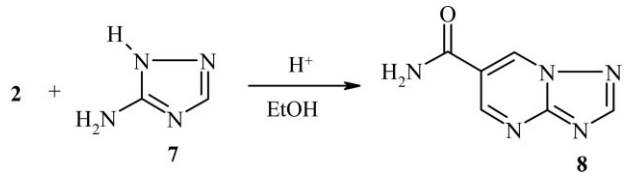
Entry	3, 4	R	Ar	Time (h)	Yield (%)[a]
1	a	H	p-Br-C_6H_4	4	80
2	b	H	p-Cl-C_6H_4	5	75
3	c	CN	H	5	78

[a] Yield refer to those of pure isolated products characterized by spectroscopic data.

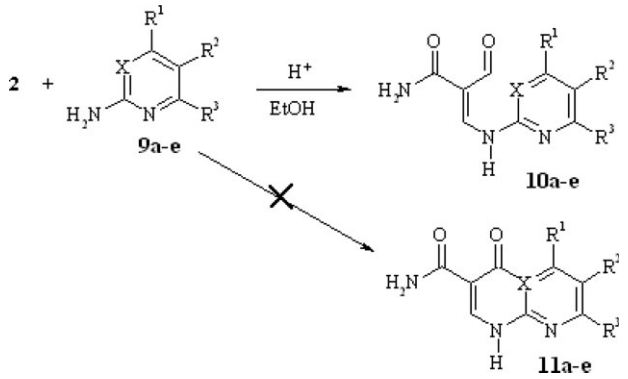
Scheme 3. Synthesis of compound **6**.



Scheme 4. Synthesis of compound **8**.



Scheme 5. Synthesis of compounds **10a-e**.



1713, 1626, 1403, cm^{-1}. ^1H NMR (300 MHz, DMSO): δ 9.34 (s, 2H, Ar-H), 9.04 (d, J = 4.8 Hz, 2H, Ar-H), 8.43 (bs, 1H, NH), 7.91 (bs, 1H, NH), 7.69 (t, J = 4.5Hz, 1H, Ar-H). ^{13}C NMR (75 MHz, DMSO): δ 169.2, 165.4, 164.1, 158.5, 157.9, 156.3, 155.4, 127.2, 115.6. *Anal*. Calcd. for $C_9H_7N_5O$ Calcd. C: 53.73; H: 3.51; N: 34.81. Found. C: 53.50; H: 3.62; N: 34.75.

[1,2,4]Triazolo[1,5-a]pyrimidine-6-carboxalic acid amide (8). Yellow solid; Yield: 82%; mp 235–237°C. IR (KBr): 3337, 3130, 3054, 1674, 1625, 1506, 1417 cm^{-1}. ^1H NMR (300 MHz, DMSO): δ 9.80 (d, J = 2.4 Hz, 1H, Ar-H), 9.25 (d, J = 2.1 Hz, 1H, Ar-H), 8.79 (s, 1H, Ar-H), 8.30 (bs, 1H, NH), 7.90 (bs, 1H, NH). ^{13}C NMR (75 MHz, DMSO): δ 163.2, 157.1, 154.9, 154.6, 137.2, 117.7. *Anal*. Calcd. for $C_6H_5N_5O$ Calcd. C: 44.17; H: 3.09; N: 42.93. Found. C: 44.20; H: 3.00; N: 42.80.

2-Formyl-3-(pyridine-2-ylamino)-acrylamide (10a). Pale yellow solid; Yield: 75%; mp 187–189°C. IR (KBr): 3371, 3057, 2873, 1666, 1628, 1594, 1408, 1152, 814, cm^{-1}. ^1H NMR (300 MHz, DMSO): δ 12.30 (d, J = 12.3 Hz, 1H, NH), 9.26 (s, 1H, CHO), 8.76 (d, J = 12.3 Hz 1H, CH), 8.39–8.30 (m, 1H, Ar-H), 8.29 (bs, 1H, NH), 7.88–7.82 (m, 1H, Ar-H), 7.57 (bs, 1H, NH), 7.45–7.41 (m, 1H, Ar-H), 7.23–7.18 (m, 1H, Ar-H). ^{13}C NMR (75 MHz, DMSO): δ 190.5, 168.1, 156.6, 149.9, 148.2, 139.1, 120.3, 112.3, 106.7. *Anal*. Calcd. for $C_9H_9N_3O_2$ Calcd. C: 56.54; H: 4.74; N: 21.98. Found. C: 56.44; H: 4.50; N: 21.70.

2-Formyl-3-(4-methyl-pyridine-2-ylamino)-acrylamide (10b). Yellow solid; Yield: 78%; mp 205–207°C. IR (KBr): 3342, 3166, 2756, 1676, 1611, 1587, 1556, 1413, 1151, 838 cm^{-1}. ^1H NMR (300 MHz, DMSO): δ 12.24 (d, J = 12.3 Hz, 1H, NH), 9.24 (s, 1H, CHO), 8.73 (d, J = 12.3 Hz 1H, CH), 8.30 (bs, 1H, NH), 8.23 (d, J = 5.1 Hz, 1H, Ar-H), 7.55 (bs, 1H, NH), 7.25 (s, 1H, Ar-H), 7.05 (dd, J = 0.9 and 4.2 Hz, 1H Ar-H), 2.33 (s, 3H, CH_3). ^{13}C NMR (75 MHz, DMSO): δ 190.5, 168.1, 156.6, 147.7, 121.4, 112.4, 106.5, 20.5. *Anal*. Calcd. for $C_{10}H_{11}N_3O_2$ Calcd. C: 58.53; H: 5.40; N: 20.48. Found. C: 58.65; H: 5.50; N: 20.35.

2-Formyl-3-(5-methyl-pyridine-2-ylamino)-acrylamide (10c). Yellow solid; Yield: 78%; mp 194–196°C. IR (KBr): 3371, 3190, 1644, 1601, 1491, 1394, 1209, 797 cm^{-1}. ^1H NMR (300 MHz, DMSO): δ 12.31 (d, J = 12.3 Hz, 1H, NH), 9.23 (s, 1H, CHO), 8.71 (d, J = 12.6 Hz 1H, CH), 8.32 (bs, 1H, NH), 8.21 (d, J = 0.9 Hz, 1H, Ar-H), 7.69–7.66 (m, 1H, Ar-H), 7.54 (bs, 1H, NH), 7.35 (d, J = 8.4 Hz, 1H Ar-H), 2.27 (s, 3H, CH_3). ^{13}C NMR (75 MHz, DMSO): δ 190.3, 168.2, 156.6, 147.9, 147.9, 139.5, 129.6, 111.8, 106.3, 17.3. *Anal*. Calcd. for $C_{10}H_{11}N_3O_2$ Calcd. C: 58.53; H: 5.40; N: 20.48. Found. C: 58.40; H: 5.45; N: 20.55.

2-Formyl-3-(6-methyl-pyridine-2-ylamino)-acrylamide (10d). Yellow solid; Yield: 80%; mp 192–194°C. IR (KBr): 3344, 3171, 2748, 1681, 1561, 1217, 809 cm^{-1}. ^1H NMR (300 MHz, DMSO): δ 12.26 (s, 1H, NH), 9.26 (s, 1H, CHO), 8.76 (bs, 1H, NH), 8.74 (d, J = 12.3 Hz 1H, CH), 7.58 (t, J = 7.8 Hz, 1H, Ar-H), 6.94 (d, J = 7.8 Hz, 1H, Ar-H), 6.73 (d, J = 8.4 Hz 1H, Ar-H), 5.55 (bs, 1H, NH), 2.52 (s, 3H, CH_3). ^{13}C NMR (75 MHz, DMSO): δ 189.9, 169.3, 158.2, 156.5, 148.9, 139.0, 120.1, 109.8, 106.4, 24.5. *Anal*. Calcd. for $C_{10}H_{11}N_3O_2$ Calcd. C: 58.53; H: 5.40; N: 20.48. Found. C: 58.45; H: 5.35; N: 20.45.

2-Formyl-3-(pyrimidine-2-ylamino)-acrylamide (10e). Off-white solid; Yield: 76%; mp 206–208°C. IR (KBr): 3360, 3177, 2764, 1677, 1654, 1576, 1560, 1205, 792 cm^{-1}. ^1H NMR (300 MHz, DMSO): δ 12.50 (d, J = 12.3 Hz, 1H, NH), 9.34 (s, 1H, CHO), 8.76–8.72 (m, 3H, CH, and Ar-H), 8.29 (bs, 1H, NH_2), 7.74 (bs, 1H, NH_2), 7.33 (t, J = 4.8 Hz, 1H, Ar-H). ^{13}C NMR (75

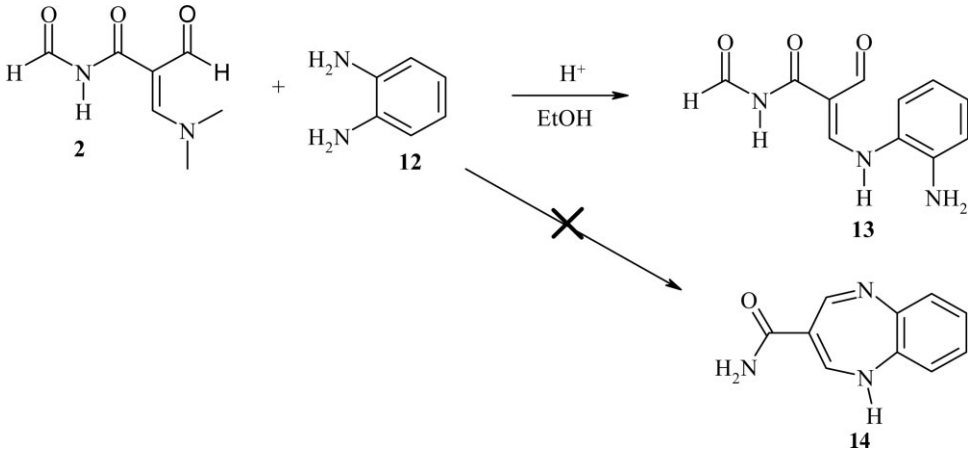
Table 3

Synthesis of compounds **10a-e**[a].

Entry	9, 10	R^1	R^2	R^3	X	Yield (%)[b]	Mp (°C)[c]
1	a	H	H	H	C	75	187–189
2	b	CH_3	H	H	C	78	205–207
3	c	H	CH_3	H	C	78	194–196
4	d	H	H	CH_3	C	80	192–194
5	e	H	H	H	N	76	206–208

[a] All spectroscopic data are compatible with the proposed structures.
[b] Isolated yields.
[c] Melting points are uncorrected.

Scheme 6. Synthesis of compound **13**.



MHz, DMSO): δ 191.1, 167.9, 158.9, 156.7, 155.5, 117.6, 107.9. *Anal*. Calcd. for $C_8H_8N_4O_2$ Calcd. C: 50.00; H: 4.20; N: 29.15. Found. C: 50.21; H: 4.00; N: 29.35.

(E)-3-(2-Aminophenylamino)-N, 2-diformylacrylamide (13). Yellow solid; Yield: 75%; mp 179–181°C. IR (KBr): 3366, 3200, 2855, 1700, 1631, 1489, 1471, 1195, 745 cm^{-1}. ^1H NMR (300 MHz, DMSO): δ 11.53 (d, J = 13.5 Hz, 1H, NH), 11.35 (d, J = 10.5 HZ, 1H, NH), 9.24 (s, 1H, CHO), 9.22 (d, J = 7.2 Hz, 1H, CHO), 8.54 (d, J = 13.8 Hz, 1H, CH), 7.35 (d, J = 6.9 Hz, 1H, Ar-H), 7.06 (t, J = 6.9 Hz, 1H, Ar-H), 6.87 (d, J = 6.6 Hz, 1H, Ar-H), 6.76 (t, J = 8.1 Hz, 1H, ArH), 5.16 (s, 2H, NH_2). ^{13}C NMR (75 MHz, DMSO): δ 190.3, 166.5, 162.2, 161.8, 140.3, 127.5, 126.2, 119.6, 118.2. *Anal*. Calcd. for $C_{11}H_{11}N_3O_3$ Calcd. C: 56.65; H: 4.75; N: 18.02. Found. C: 56.50; H: 4.80; N: 18.25.

Acknowledgments. This work was supported by UGC, New Delhi, India. The authors thank Dr. V. B. Gaikwad for his valuable cooperation.

REFERENCES AND NOTES

[1] Novinson, T.; Hanson, R.; Dimmitt, M.; Simon, I.; Robin, R.; Brien, D. J Med Chem 1974, 17, 645.

[2] Novinson, T.; Miller, J.; Scholten, M.; Simon, I.; Robin, R.; Brien, D.; Mayer. R. J Med Chem 1975, 18, 460.

[3] Senga, K.; Novinson, T.; Wilson, H.; Robin, R. J Med Chem 1981, 24, 610.

[4] Luque, F.; Fernandez-Ramos, C.; Entrala, E.; Rosales, M. J.; Navarro, J. A.; Romaro, M. A.; Salas, J. M.; Sanchez-Moreno, M. Comp Biochem Physiol C 2000, 126, 39.

[5] Berman, J. D.; Chulay, J. D.; Hendricks, L. D.; Oster, C. N. J Infect 1983, 31, 459.

[6] Veiga, J. P.; Rosa, T. T.; Kimachi, T.; Wolf, E. R.; Sampaio, R. N.; Gagliardi, A. R. T.; Junqueira, L. F.; Costa, J. M. L.; Marsden, P. D. Rev Inst Med Trop Sao Paulo 1985, 27, 665.

[7] Ram, V. J.; Haque, N.; Guru, P. Eur J Med Chem 1992, 27, 851.

[8] Reichardt, C.; Kermer, W. D. Synthesis 1970, 538.

[9] Breaux, E. J.; Zwikelmaier, K. E. J Heterocycl Chem 1981, 18, 183.

[10] Stanovnik, B.; Svete, J. Chem Rev 2004, 104, 2433.

[11] Pirc, S.; Bevk, D.; Golobic, A.; Stanovnik, B.; Svete, J. Helv Chim Acta 2006, 89, 30.

[12] Bratusek, U.; Meden, A.; Svete, J.; Stanovnik, B. ARKIVOC, 2003, (V), 77.

[13] Jachak, M.; Kriessmamm, U.; Mittelbach, M.; Junek, H. Monatsh Chem 1993, 124, 199.

[14] Jachak, M.; Mittelbach, M.; Junek, H. Heterocycles 1993, 36, 2281.

[15] Leimgruder, W.; Weigele, M. U.S. Patent 3,689,498, 1972; Chem Abstr 1972, 77, 140130g.

[16] Leimgruder, W.; Weigele, M. U.S. Pat 3,792,076, 1974; Chem Abstr 1974, 80, 96011e.

[17] Leimgruder, W.; Weigele, M. U.S. Pat 3,901,888, 1975; Chem Abstr 1976, 84, 4996m.

[18] Jachak, M.; Avhale, A.; Tantak, C.; Toche, R.; Reidlinger, C.; Stadlbauer, W. J Heterocycl Chem 2005, 42, 1311.

[19] Jachak, M.; Avhale, A.; Medhane, V.; Toche, R. J Heterocycl Chem 2006, 43, 1169.

[20] Jachak, M.; Avhale, A.; Toche, R.; Sabnis, R. J Heterocycl Chem 2007, 44, 343.