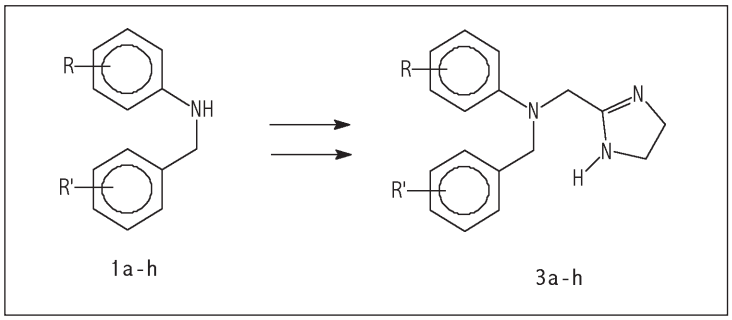
P. Dash, D. P. Kudav and J. A. Parihar*

Department of Chemistry, University of Mumbai, Vidyanagari, Santacruz (E), Mumbai-400098, India.
E-mail: *japarihar@rediffmail.com*

Received July 18, 2005



Different *N*-benzyl anilines were *N*-alkylated with chloroacetonitrile to give the corresponding nitriles, which were subsequently condensed with ethylenediamine in the presence of thioacetamide to afford the corresponding title antazoline derivatives.

J. Heterocyclic Chem., **43**, 401 (2006).

Imidazoline derivatives exhibit significant biological and pharmacological activities including antihypertensive [1,2], antihyperglycemic [3-7], antidepressive [8], antihypercholesterolemic [9] and anti-inflammatory activities [10]. Due to these practical applications, we have expended considerable effort in the preparation of new imidazoline derivatives. Recently we have reported the synthesis 2-imidazoline analogs of phentolamine by the alkylation of diphenylamines with chloroacetonitrile and subsequent cyclisation of aminonitriles with ethylenediamine in presence of thioacetamide [11]. Antazoline is a well-known drug of the imdazoline family having antihistaminic activity [12-13], ambecidal activity [14] and antiarrhyhmic activity [15]. Earlier synthesis of antazoline starts the cyanomethylation of the *N*-benzylaniline with NaCN and formaldehyde requiring a closed vessel and long reaction period [16]. In this article we wish to report the synthesis of some novel antazoline derivatives using alkylation of *N*-benzylanilines with chloroacetonitrile as a key step.

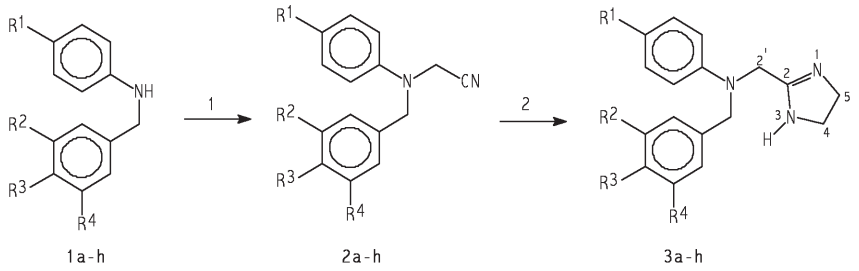
Towards this end the alkylation of *N*-benzylaniline **1a** with chloroacetonitrile was undertaken. All our attempts to carry out the reaction in CH_3CN, DMF, DMSO and THF as reaction solvents using different bases such as K_2CO_3, KF, DMAP and $Et(^iPr)_2N$ proved unsuccessful. Although the alkylation of **1a** with $ClCH_2CN$ and NaI in presence of KF, DMAP, $Et(^iPr)_2N$ in HMPA at 100 °C afforded the corresponding nitrile **2a**, K_2CO_3 in HMPA in presence of NaI proved be the most effective reaction condition and **2a** was obtained in 84% yield after the column chromatographic purification (Table 1). This was unlike our earlier observation [11] wherein the *N*-alkylation of diphenyl amine with chloroacetonitrile in the last condition (K_2CO_3/NaI/HMPA) failed to give any *N*-alkylated product. Seebach *et al*. [17] have used DMPU as a good and safe alternative for HMPA for the *N*-alkylation of less reactive amines. Hence we thought to investigate the influence of DMPU for the *N*-alkylation **1a** with chloroacetonitrile. Heating *N*-benzylaniline **1a** with chloroacetonitrile and NaI in the presence of K_2CO_3 in DMPU at 100 °C for 3 h gave **2a** in 64% yield after the column chromatographic purification. The structure of **2a** was ascertained from its elemental analysis and spectroscopic data. The IR spectrum of **2a** displayed C-N stretching at 2255 cm^{-1} for the CN group and ^{1}H-NMR spectrum displayed two 2H singlets for CH_2-CN and CH_2-Ar at δ_H 4.53 and δ_H 4.11 respectively thus confirming the alkylation of **1a** with chloroacetonitrile. These two reaction conditions (K_2CO_3, NaI, HMPA and K_2CO_3, NaI, DMPU) were then utilized for the *N*-alkylation of other *N*-benzylanilines with chloroacetonitrile to give the corresponding aminoacetonitriles **2b-h** in 80-88% and 61-72% yields respectively (Scheme 1, Table 2). The aminoacetonitriles **2a-h** thus obtained were condensed by refluxing with ethylenediamine in the presence of a catalytic amount of thioacetamide for 3 h to afford the corresponding analytically pure title compounds **3a-h** in 75-80% yields (Scheme 1, Table 2). The structures of **3a-h** were ascertained from their elemental

Table 1

Tested alkylation conditions for the reaction of *N*-benzylaniline (**1a**) with $ClCH_2CN$.

Solvent	Base	Additive	Temp (°C)	Time (h)	Yield (%)
HMPA	K_2CO_3	NaI	100	0.75	84
	KF	NaI	100	5	51
	DMAP	NaI	100	6	19
	$Et(^iPr)_2N$	NaI	100	6	24
DMPU	K_2CO_3	NaI	100	3	64

Scheme 1



Reagents and conditions: 1) Chloroacetonitrile, K_2CO_3, NaI, HMPA/DMPU, 100∞C. 2) ethylenediamine, thioacetamide, reflux.

Synthesis of antazoline derivatives.

Table 2

Synthesized aminoacetonitriles and antazoline derivatives.

Compound	R^1	R^2	R^3	R^4	Yield[a] / %
2a	H	H	H	H	84[b] (64)[c]
2b	OCH_3	H	H	H	87[b] (71)[c]
2c	CH_3	H	H	H	81[b] (61)[c]
2d	H	H	OCH_3	H	85[b] (67)[c]
2e	H	OCH_3	OCH_3	H	88[b] (72)[c]
2f	H	OCH_3	OCH_3	OCH_3	84[b] (68)[c]
2g	CH_3	H	OCH_3	H	82[b] (66)[c]
2h	Cl	H	OCH_3	H	80[b] (65)[c]
3a	H	H	H	H	77
3b	OCH_3	H	H	H	79
3c	CH_3	H	H	H	75
3d	H	H	OCH_3	H	77
3e	H	OCH_3	OCH_3	H	80
3f	H	OCH_3	OCH_3	OCH_3	76
3g	CH_3	H	OCH_3	H	79
3h	Cl	H	OCH_3	H	78

[a] Yield refers to purified product; [b] Yield obtained with K_2CO_3, NaI, HMPA; Yield obtained with K_2CO_3, NaI, DMPU.

analysis and spectroscopic data. The ^{1}H-NMR spectrum of **3e** displayed a 4H singlet at δ_H 3.56 for N-CH_2-CH_2-N, two 3H singlets at δ_H 3.81 and δ_H 3.86 for two OCH_3 and two 2H singlets for CH_2-C=N and CH_2-Ar at δ_H 4.53 and δ_H 4.15 respectively. The ^{13}C-NMR spectrum of **3e** displayed a signal at δ_C 166.6 for C=N and MS showed molecular ion peak at m/z = 325. In the ^{1}H-^{13}C gHSQC spectrum of **3e** a signal at δ_C 50.2 showed correlation with δ_H 4.53 as well as δ_H 3.56 and a signal at δ_C 55.5 showed correlation with δ_H 4.15. Based on this, a signal at δ_C 50.2 was assigned for C-4 and C-5 of imidazoline ring and C-2' and a signal at δ_C 55.5 was assigned for Ar-*C*H_2. Use of CS_2 [18] and P_2S_5 [19] instead of thioacetamide as H_2S source gives impure compound, which requires complicated purification. The yields of the compounds synthesized are listed in Table 2.

In conclusion, *N*-benzyl anilines were *N*-alkylated with chloroacetonitrile in presence of K_2CO_3 and NaI in HMPA to give the corresponding nitriles **1a-h**. Carcinogenic HMPA was also replaced by DMPU, though the yields obtained in HMPA were slightly better. Nitriles **2a-h** were subsequently condensed with ethylenediamine in the presence of thioacetamide to afford the corresponding title compounds **3a-h** in good yields.

EXPERIMENTAL

General Procedure for the Synthesis of Aminoacetonitrile **2a-h**.

A mixture of *N*-benzylaniline (10 mmol) **1a-h**, chloroacetonitrile (15 mmol), anhyd. K_2CO_3 (10 mmol) and NaI (10 mmol) in dry HMPA (**caution**!)/DMPU (7 cm^3) was heated at 100 °C for 45 min/3 h. The reaction mixture was diluted with water and extracted with EtOAc (4 × 50 cm^3). The combined EtOAc extracts were washed with water (3 × 50 cm^3) and then dried (anhydrous Na_2SO_4). Evaporation of the solvent gave a brown residue which was purified by column chromatography [silica gel, Hexane:$CHCl_3$ (50:50)] to afford the corresponding aminoacetonitrile **2a-h**.

[Benzyl(phenyl)amino]acetonitrile (**2a**).

Pale yellow oil; IR (oil film): ν 2255 (CN) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 60 MHz) δ 4.11 (2H, s, Ar-CH_2), 4.53 (2H, s, CH_2-CN), 6.54-7.47 (10H, m, Ar-H).

Anal. Calcd. for $C_{15}H_{14}N_2$: C, 81.05; H, 6.35; N, 12.60. Found: C, 80.96; H, 6.39; N, 12.65.

[Benzyl(4-methoxyphenyl)amino]acetonitrile (**2b**).

Pale yellow oil; IR (oil film) ν 2252 (CN) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 60 MHz) δ 3.69 (3H, s, OCH_3), 4.01 (2H, s, Ar-CH_2), 4.42 (2H, s, CH_2-CN), 6.66-7.42 (9H, m, Ar-H); MS (EI) *m/z* (relative intensity): 252 (M^+, 10%), 107 (18), 91(100).

Anal. Calcd. for $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39; N, 11.10. Found: C, 76.07; H, 6.44; N, 11.14.

[Benzyl(4-methylphenyl)amino]acetonitrile (**2c**).

Pale yellow oil; IR (oil film) ν 2257 (CN) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 60 MHz) δ 2.25 (3H, s, CH_3), 4.13 (2H, s, Ar-CH_2), 4.49 (2H, s, CH_2-CN), 6.50-7.45 (9H, m, Ar-H); MS (EI) *m/z* (relative intensity): 236 (M^+, 9%), 91 (100).

Anal. Calcd. for $C_{16}H_{16}N_2$: C, 81.32; H, 6.82; N, 11.85. Found: C, 81.41; H, 6.78; N, 11.80.

[(4-Methoxybenzyl)(phenyl)amino]acetonitrile (**2d**).

Colourless solid: mp 84 °C; IR (KBr) ν 2251 (CN) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 3.80 (3H, s, OCH_3), 4.02 (2H, s, Ar-CH_2), 4.42 (2H, s, CH_2-CN), 6.88 (2H, d, *J* = 8.7, H-3 & H-5 of Bn group), 6.92-6.98 (3H, m, H-2, H-6 & H-4 of Ph group), 7.23 (2H, d, *J* = 8.7, H-2 & H-6 of Bn group), 7.30 (2H, dd, *J* = 7.4 & 7.1, H-3 & H-5 of Ph group).

Anal. Calcd. for $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39; N, 11.10. Found: C, 76.26; H, 6.35; N, 11.06.

[(3,4-Dimethoxybenzyl)(phenyl)amino]acetonitrile (**2e**).

Colourless solid: mp 75-77 °C; IR (KBr) ν 2260 (CN) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 60 MHz) δ 3.71 (6H, combined singlet, OCH_3), 4.05 (2H, s, Ar-CH_2), 4.50 (2H, s, CH_2-CN), 6.53-7.44 (8H, m, Ar-H).

Anal Calcd. for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92. Found: C, 72.23; H, 6.45; N, 9.96.

[Phenyl(3,4,5-trimethoxybenzyl)amino]acetonitrile (**2f**).

Colourless solid: mp 88 °C; IR (KBr) ν 2256 (CN) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 60 MHz) δ 3.69 (9H, combined singlet, OCH_3), 4.00 (2H, s, Ar-CH_2), 4.41 (2H, s, CH_2-CN), 6.65-7.40 (7H, m, Ar-H).

Anal. Calcd. for $C_{18}H_{20}N_2O_3$: C, 69.21; H, 6.45; N, 8.97. Found: C, 69.29; H, 6.41; N, 8.95.

[(4-Methoxybenzyl)(4-methylphenyl)amino]acetonitrile (**2g**).

Colourless solid: mp 94; IR (KBr) ν 2260 (CN) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 60 MHz) δ 2.23 (3H, s, CH_3), 3.70 (3H, s, OCH_3), 4.12 (2H, s, Ar-CH_2), 4.50 (2H, s, CH_2-CN), 6.52-7.30 (8H, m, Ar-H); MS (EI) *m/z* (relative intensity): 266 (M^+, 4%), 121 (100), 91 (10).

Anal. Calcd. for $C_{17}H_{18}N_2O$: C, 76.66; H, 6.81; N, 10.52. Found: C, 76.56; H, 6.85; N, 10.55.

[(4-Chlorophenyl)(4-methoxybenzyl)amino]acetonitrile (**2h**).

Colourless solid: mp 65 °C; IR (KBr) ν 2258 (CN) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 3.81 (3H, s, OCH_3), 4.01 (2H, s, Ar-CH_2), 4.40 (2H, s, CH_2-CN), 6.88 (2H, d, *J* = 9.0, H-3 & H-5 of Bn group), 6.91 (2H, d, *J* = 8.9, H-2 & H-6 of Ph group), 7.23 (2H, d, *J* = 9.0, H-2 & H-6 of Bn group), 7.27 (2H, d, *J* = 8.9, H-3 & H-5 of Ph group).

Anal. Calcd. for $C_{16}H_{15}ClN_2O$: C, 67.02; H, 5.27; Cl, 12.36; N, 9.77. Found: C, 67.13; H, 5.23; Cl, 12.33; N, 9.74.

General Procedure for the Synthesis of Antazoline Derivatives **3a-h**.

A mixture of aminoacetonitrile **2a-h** (10 mmol), thioacetamide (1 mmol) in ethylenediamine (7 cm^3) was refluxed with stirring for 3 h. The reaction mixture was diluted with water and extracted with $CHCl_3$ (4 × 50 cm^3). The combined $CHCl_3$ extracts were washed with water (3 × 50 cm^3) and then dried (anhydrous Na_2SO_4). Evaporation of the solvent followed by trituration of the residue obtained with petroleum ether (60:80) afforded the corresponding analytically pure antazoline derivatives **3a-h** which were then further purified by recrystalization with $CHCl_3$ and hexane.

Benzyl(4,5-dihydro-1*H*-imidazol-2-ylmethyl)phenylamine (**3a**).

Colourless solid: mp 120 °C (Lit. [16] mp 120 °C); IR (KBr) ν 3215 (N-H str.) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 60 MHz) δ 3.52 (4H, s), 4.00 (2H, s, Ar-CH_2), 4.55 (2H, s, CH_2-C=N), 6.95-7.43 (10H, m, Ar-H).

Anal. Calcd. for $C_{17}H_{19}N_3$: C, 76.95; H, 7.22; N, 15.84. Found: C, 76.88; H, 7.25; N, 15.80.

Benzyl(4,5-dihydro-1*H*-imidazol-2-ylmethyl)(4-methoxyphenyl)amine (**3b**)).

Colourless solid: mp 107 °C; IR (KBr) ν 3210 (N-H str.) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 3.55 (4H, s), 3.73 (3H, s, OCH_3), 4.10 (2H, s, Ar-CH_2), 4.56 (2H, s, CH_2-C=N), 6.78-7.00 (4H, m, Ar-H), 7.22-7.32 (5H, m, Ar-H).

Anal. Calcd. for $C_{18}H_{21}N_3O$: C, 73.19; H, 7.17; N, 14.23. Found: C, 73.28; H, 7.13; N, 14.20.

Benzyl(4,5-dihydro-1*H*-imidazol-2-ylmethyl)(4-methylphenyl)amine (**3c**)).

Colourless solid: mp 93 °C; IR (KBr) ν 3220 (N-H str.) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.24 (3H, s, CH_3), 3.54 (4H, s), 4.13 (2H, s, Ar-CH_2), 4.54 (2H, s, CH_2-C=N), 6.71 (2H, d, *J* = 8.2, H-2 & H-6 of Ph group), 7.1 (2H, d, *J* = 8.2, H-3 & H-5 of Ph group), 7.20-7.31 (5H, m, Ar-H of Bn group); MS (EI) *m/z* (relative intensity): 279 (M^+, 6%), 91 (61), 84 (100).

Anal. Calcd. for $C_{18}H_{21}N_3$: C, 77.38; H, 7.58; N, 15.04; found: C, 77.30; H, 7.61; N, 15.09.

(4,5-Dihydro-1*H*-imidazol-2-ylmethyl)(4-methoxybenzyl)-phenylamine (**3d**).

Colourless solid: mp 116 °C; IR (KBr) ν 3250 (N-H str.) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 3.55 (4H, s), 3.79 (3H, s, OCH_3), 4.14 (2H, s, Ar-CH_2), 4.53 (2H, s, CH_2-C=N), 6.78 (1H, t, *J* = 7.5, H-4 of Ph group), 6.84-6.96 (4H, m, Ar-H), 7.16 (2H, d, *J* = 7.8, H-2 & H-6 of Bn group), 7.23 (2H, t, *J* = 7.5, H-3 & H-5 of Ph group).

Anal Calcd. for $C_{18}H_{21}N_3O$: C, 73.19; H, 7.17; N, 14.23. Found: C, 73.30; H, 7.12; N, 14.20.

(4,5-Dihydro-1*H*-imidazol-2-ylmethyl)(3,4-dimethoxybenzyl)-phenylamine (**3e**).

Colourless solid: mp 115 °C; IR (KBr) ν 3300 (N-H str.) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 3.56 (4H, s), 3.81 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 4.15 (2H, s, Ar-CH_2), 4.53 (2H, s, CH_2-C=N), 6.76-6.84 (6H, m, Ar-H), 7.24 (2H, t, *J* = 7.7, H-3 & H-5 of Ph group); ^{13}C-NMR ($CDCl_3$, 400 MHz): δ 50.2 (C-4, C-5 of imidazoline ring and C-2'), 55.5 (Ar-*C*H_2), 55.8 (OCH_3), 55.9 (OCH_3), 110.3 (CH), 111.3 (CH), 113.2 (C-2, C-6 of phenyl ring), 118.1 (CH), 119.2 (CH), 129.4 (C-3, C-5 of phenyl ring), 130.4 (C), 148.2 (C), 148.7, 149.2 (C), 166.6 (C=N); MS (EI) *m/z* (relative intensity): 325 (M^+, 8%), 241 (65), 150 (48), 82 (100).

Anal. Calcd. for $C_{19}H_{23}N_3O_2$: C, 70.13; H, 7.12; N, 12.91. Found: C, 70.03; H, 7.16; N, 12.95.

(4,5-Dihydro-1*H*-imidazol-2-ylmethyl)phenyl(3,4,5-trimethoxybenzyl)amine (**3f**).

Colourless solid: mp 117 °C; IR (KBr) ν 3220 (N-H str.) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 3.57 (4H, s), 3.78 (6H, s, OCH_3), 3.82 (3H, s, OCH_3), 4.17 (2H, s, Ar-CH_2), 4.51 (2H, s, CH_2-C=N), 6.45 (2H, s, H-2 & H-6 of Bn group), 6.79 (3H, m, H-2, H-4 & H-6 of Ph group), 7.22 (2H, t, *J* = 7.7, H-3 & H-5 of Ph group).

Anal. Calcd. for $C_{20}H_{25}N_3O_3$: C, 67.58; H, 7.09; N, 11.82; found: C, 67.67; H, 7.06; N, 11.87.

(4,5-Dihydro-1*H*-imidazol-2-ylmethyl)(4-methoxybenzyl)(4-methylphenyl)amine (**3g**).

Colourless solid: mp 104 °C; IR (KBr) ν 3230 (N-H str.) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 2.25 (3H, s, CH_3), 3.54 (4H, s), 3.78 (3H, s, OCH_3), 4.10 (2H, s, Ar-CH_2), 4.47 (2H, s, CH_2-C=N), 6.74 (2H, d, *J* = 8.2, H-2 & H-6 of Ph group), 6.84 (2H, d, *J* = 8.3, H-3 & H-5 of Bn group), 7.04 (2H, d, *J* = 8.2, H-3 & H-5 of Ph group), 7.15 (2H, d, *J* = 8.3, H-2 & H-6 of Bn group); MS (EI) *m/z* (relative intensity): 309 (M^+, 1%), 121 (40), 84 (100).

Anal. Calcd. for $C_{19}H_{23}N_3O$: C, 73.76; H, 7.49; N, 13.58. Found: C, 73.66; H, 7.46; N, 13.54.

(4-Chlorophenyl)(4,5-dihydro-1*H*-imidazol-2-ylmethyl)(4-methoxybenzyl)amine (**3h**).

Colourless solid: mp 103 °C; IR (KBr) ν 3200 (N-H str.) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 3.56 (4H, s), 3.78 (3H, s, OCH_3), 4.12 (2H, s, Ar-CH_2), 4.49 (2H, s, CH_2-C=N), 6.71 (2H, d, *J* = 8.2, H-2 & H-6 of Ph group), 6.84 (2H, d, *J* = 8.3, H-3 & H-5 of Bn group), 7.09-7.25 (4H, m, Ar-H); ^{13}C-NMR ($CDCl_3$, 400 MHz): δ = 50.3 (C-4, C-5 of imidazoline ring and C-2'), 55.2 (Ar-*C*H_2), 55.3 (OCH_3), 114.2 (2 CH), 114.4 (2 CH), 122.9 (C), 128.1 (2 CH), 129.1 (2 CH), 129.4 (C), 147.2 (C), 158.9 (C), 167 (C=N).

Anal. Calcd. for $C_{18}H_{20}N_3OCl$: C, 65.55; H, 6.11; Cl, 10.75; N, 12.74. Found: C, 65.66; H, 6.08; Cl, 10.72; N, 12.70.

Acknowledgements.

One of the authors (PD) is thankful to the G. D. Gokhale Charitable Trust for the financial.

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