Alkylation of diphenylamines with chloroacetonitrile: a new entry to phentolamine analogues

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The alkylation of diphenylamines with chloroacetonitrile followed by annulation with ethylenediamine gave 2-imidazoline analogues of phentolamine.

Keywords: diphenylamines, chloroacetonitrile, 2-imidazolines, phentolamine, annulation

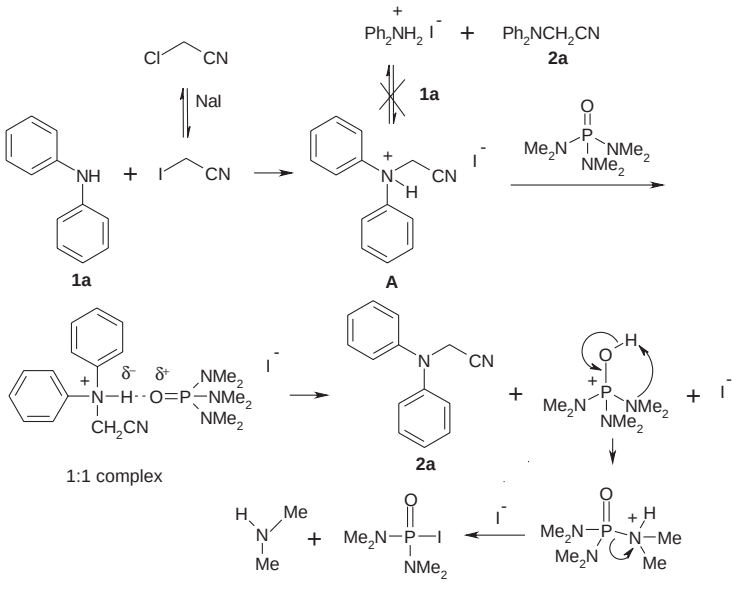
The wide biological activity of 2-substituted 2-imidazolines has stimulated considerable synthetic work on this heterocycle. Phentolamine is well known drug of this family possessing antiallergic activity[1] and α-adrenergic activity.[2] Previous syntheses of this well known drug start with the cyanomethylation of the *N*-4-methylphenyl-*N*-3-acetoxyphenylamine with NaCN and formaldehyde requiring a closed vessel.[3] In other reported methods, the *N*-alkylation of *N*-4-methylphenyl-*N*-3-hydroxyphenylamine with 2-chloromethyl-4,5-dihydro-1*H*-2-imidazole hydrochloride requires rather harsh conditions[3,4] (130–150 °C, closed vessel in some cases). Moreover the phentolamine obtained by this method requires a complicated purification.[3] Another logical route, the *N*-alkylation diphenylamines with $ClCH_2CN$, has not yet been explored for the synthesis of the title compounds.

The alkylation of diphenylamine **1a** with $ClCH_2CN$ was undertaken first. As shown in Table 1, all our attempts to alkylate **1a** with $ClCH_2CN$ in CH_3CN, DMF, DMSO and THF as reaction medium were unsatisfactory. 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 *N*-alkylated nitrile **2a**, the alkylation in absence of any base other than diphenylamine (substrate) itself in HMPA was most suitable. The structure of **2a** was ascertained from its elemental and spectroscopic data. The IR spectrum of **2a** displayed C–N str. at 2260 cm^{-1} for CN group and the ^{1}H-NMR spectrum displayed a two-proton singlet at δ_H 4.4 (CH_2-CN) thus confirming the alkylation of **1a** with chloroacetonitrile. The yield of **2a** exceeds 50% even though the *N*-alkylation of **1a** is carried out in absence of any base other than diphenylamine (substrate) itself. This may be explained on the basis of formation of 1:1 complex[5] of **A** with HMPA and thus preventing the formation of equilibrium with another molecule of diphenylammonium iodide (Scheme 1). This standardised protocol was then utilised for the alkylation of other diphenylamine derivatives with

Table 1 Screening of the alkylation of diphenylamine **(1a)** with $ClCH_2CN$

Solvent	Base	Additive	Temp/°C	Time/h	Yield/%
CH_3CN	K_2CO_3	NaI	Reflux	40	–
	KF	NaI	Reflux	40	–
	DMAP	NaI	Reflux	40	–
	$Et(^iPr)_2N$	NaI	Reflux	40	–
	-	NaI	Reflux	40	–
DMF	K_2CO_3	NaI	100	40	–
	KF	NaI	100	40	–
	DMAP	NaI	100	40	–
	$Et(^iPr)_2N$	NaI	100	40	–
	–	NaI	100	40	8[a]
	NaH	–	0–80	40	–
DMSO	K_2CO_3	NaI	100	40	–
	KF	NaI	100	40	–
	DMAP	NaI	100	40	–
	$Et(^iPr)_2N$	NaI	100	40	–
	–	NaI	100	40	13[a]
THF	NaH	–	0-reflux	40	–
HMPA	K_2CO_3	NaI	100	40	-
	KF	NaI	100	25	45
	DMAP	NaI	100	32	26
	$Et(^iPr)_2N$	NaI	100	32	36
	–	NaI	100	24	56

[a]Based on GC analysis



Scheme 1 Alkylation of **1a** with $ClCH_2CN$ in presence of NaI in HMPA (without any base).

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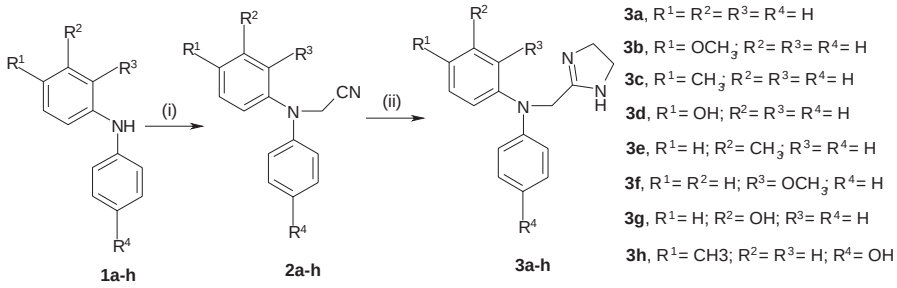
Table 2 Synthesis of phentolamine analogues

Compound	R^1	R^2	R^3	R^4	Reaction period/h	Yield[a]/%
2a	H	H	H	H	24	56 (16)[b]
2b	OCH_3	H	H	H	20	70 (10)[b]
2c	CH_3	H	H	H	22	68 (12)[b]
2d	OH	H	H	H	17	76
2e	H	CH_3	H	H	20	62 (15)[b]
2f	H	H	OCH_3	H	20	68 (11)[b]
2g	H	OH	H	H	16	69
2h	CH_3	H	H	OH	20	72
3a	H	H	H	H	3	78
3b	OCH_3	H	H	H	3	77
3c	CH_3	H	H	H	3	78
3d	OH	H	H	H	3	72
3e	H	CH_3	H	H	3	78
3f	H	H	OCH_3	H	3	79
3g	H	OH	H	H	3	70
3h	CH_3	H	H	OH	3	72

[a]Yield refers to purified product.
[b]% of starting material recovered.



Scheme 2 Synthesis of phentolamine analogues. Reagents and conditions: (i) $ClCH_2CN$, NaI, HMPA, 100 °C, 16–24 h. (ii) Ethylenediamine, thioacetamide, reflux 3 h.

$ClCH_2$–CN to give the corresponding *N*-alkylated compounds **2b–h** in reasonably good yields (56–74%). The *N*-alkylated nitriles **2a–h** thus obtained were then refluxed in ethylenediamine in presence of a catalytic amount of thioacetamide for 3 h to undergo annulation to afford the corresponding analytically pure title compounds **3a–h** (Scheme 2) in attractive yields. The structures of **3a–h** were ascertained from their elemental and spectroscopic data. The PMR spectrum of **3a–h** displayed a four proton singlet for the imidazoline ring and a two proton singlet for CH_2–N. Use of CS_2[6] and P_2S_5[7] instead of thioacetamide as H_2S source gave impure products, which required a complicated purification. The physical constant and yield of the compounds synthesised are listed in Table 2. Unlike the earlier reported methods[3,8] the protection of OH group in case of alkylation of **1d**, **1g** and **1h** with $ClCH_2CN$ for the formation of **2d**, **2g** and **2h** is not required in our methodology.

In conclusion, the present work provides a new synthesis of the title compounds **3a–h** which involves *N*-alkylation of **1a–h** respectively with $ClCH_2CN$ followed by annulation of **2a–h** with ethylenediamine in the presence of a catalytic amount of thioacetamide. The synthesis of title compounds **3a–h** is short, general, and utilises easily accessible materials and the yields are also attractive.

Experimental

General procedure for the synthesis of N-alkylated nitrile **2**: A mixture of diphenylamine (10 mmole) **1**, $ClCH_2CN$ (15 mmole), and NaI (10 mmole) in dry HMPA (7 cm^3) was heated on a steam bath for 16–24 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 *N*-alkylated nitrile **2**.

N,N-Diphenylamino acetonitrile **2a**: Pale yellow oil; IR (oil film): 2260 (CN) cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz): δ = 4.4 (2H, s, CH_2–CN), 6.66–7.4 (10H, m, Ar–H); Anal. calcd. for $C_{14}H_{12}N_2$: C, 80.74; H, 5.81; N, 13.45. Found: C, 80.82; H, 5.79; N, 13.40.

N-4-Methoxyphenyl-N-phenylamino acetonitrile **2b**: White solid: m.p. 94 °C; IR (KBr): 2256 (CN) cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz): δ = 3.8 (3H, s, OCH_3), 4.4 (2H, s, CH_2–CN), 6.5–7.33 (9H, m, Ar–H); Anal. calcd. for $C_{15}H_{14}N_2O$: C, 75.61; H, 5.92; N, 11.76. Found: C, 75.51; H, 5.95; N, 11.80.

N-4-Methylphenyl-N-phenylamino acetonitrile **2c**: White solid: m.p. 81 °C; IR (KBr): 2255 (CN) cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz): δ = 2.32 (3H, s, CH_3), 4.5 (2H, s, CH_2–CN), 6.66–7.33 (9H, m, Ar–H); Anal. calcd. for $C_{15}H_{14}N_2$: C, 81.05; H, 6.35; N, 12.60. Found: C, 81.15; H, 6.31; N, 12.54.

N-4-Hydroxyphenyl-N-phenylamino acetonitrile **2d**: White solid: m.p. 100 °C; IR (KBr): 2253 (CN) cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): δ = 4.70 (2H, s, CH_2–CN), 6.73 (2H, d, *J* = 7.8 Hz), 6.89–6.83 (3H, m), 7.00 (2H, d, *J* = 7.8 Hz), 7.20 (2H, dd, *J* = 7.33, 7.43), 9.50 (1H, br s, OH); Anal. calcd. for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.39; N, 12.49. Found: C, 74.89; H, 5.43; N, 12.54.

N-3-Methylphenyl-N-phenylamino acetonitrile **2e**: Pale yellow oil; IR (oil film): 2255 (CN) cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz): δ = 2.30 (3H, s, CH_3), 4.45 (2H, s, CH_2–CN), 6.75–7.50 (9H, m, Ar–H); Anal. calcd. for $C_{15}H_{14}N_2$: C, 81.05; H, 6.35; N, 12.60. Found: C, 81.14; H, 6.32; N, 12.54.

N-2-Methoxylphenyl-N-phenylamino acetonitrile **2f**: Pale yellow oil; IR (oil film): 2257 (CN) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ = 3.82 (3H, s, OCH_3), 4.45 (2H, s, CH_2–CN), 6.74 (2H, dd, *J* = 1.02, 8.69), 6.86 (1H, t, *J* = 7.21), 6.94–7.02 (2H, m), 7.20-7.30 (4H, m); Anal. calcd. for $C_{15}H_{14}N_2O$: C, 75.61; H, 5.92; N, 11.76. Found: C, 75.72; H, 5.88; N, 11.70.

N-3-Hydroxyphenyl-N-phenylamino acetonitrile **2g**: Light green oil; IR (oil film): 2252 (CN) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ = 4.50 (2H, s, CH_2–CN), 5.17 (1H, br s, OH), 6.44–6.56 (3H, m), 7.10–7.19 (4H, m), 7.36 (2H, dd, *J* = 7.82, 8.10); Anal. calcd. for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.39; N, 12.49. Found: C, 75.09; H, 5.34; N, 12.43.

N-3-Hydroxyphenyl-N-4-methylphenyl amino acetonitrile **2h**: Light green oil; IR (oil film): 2250 (CN) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ = 2.35 (3H, s, CH_3), 4.51 (2H, s, CH_2–CN), 5.19 (1H, br s,

OH), 6.42–6.55 (3H, m), 7.10 (2H, d, *J* = 7.82); 7.19 (1H, dd, *J* = 7.30, 7.43); 7.30 (2H, d, *J* = 7.82); Anal. calcd. for $C_{15}H_{14}N_2O$: C, 75.61; H, 5.92; N, 11.76. Found: C, 75.50; H, 5.95; N, 11.83.

General procedure for the synthesis of **3**: A mixture of *N*-alkylated nitrile **2** (10 mmole), thioacetamide (1 mmole) 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 pet. ether (60 : 80) afforded the corresponding pure **3** which was then further purified by recrystallisation with chloroform and hexane.

N-(4,5-Dihydro-1H-2-imidazolylmethyl)-N, N-diphenylamine **3a**: White solid: m.p. 150 °C (Lit.[9] mp 149–51 °C); IR (KBr): 3220 (N–H str.) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ = 3.57 (4H, s), 4.56 (2H, s, CH_2–C=N), 6.96–7.08 (6H, m, Ar–H), 7.24–7.32 (4H, m, Ar–H); Anal. calcd. for $C_{16}H_{17}N_3$: C, 76.46; H, 6.82; N, 16.72. Found: C, 76.38; H, 6.85; N, 16.77.

N-(4,5-Dihydro-1H-2-imidazolylmethyl)-N-4-methoxyphenyl-N-phenylamine **3b**: White solid: m.p. 107 °C (Lit.[10] m.p. 109–111°C); IR (KBr): 3210 (N–H str.) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ = 3.59 (4H, s), 3.80 (3H, s, OCH_3); 4.48 (2H, s, CH_2–C=N), 6.80–6.85 (3H, m, Ar–H), 6.88 (2H, d, *J* = 8.97), 7.11 (2H, d, *J* = 8.97), 7.19 (2H, dd, *J* = 7.68, 8.10); Anal. calcd. for $C_{17}H_{19}N_3O$: C, 72.57; H, 6.81; N, 14.93. Found: C, 72.67; H, 6.78; N, 14.89.

N-(4,5-Dihydro-1H-2-imidazolylmethyl)-N-4-methylphenyl-N-phenylamine **3c**: White solid: m.p. 130 °C; IR (KBr): 3250 (N–H str.) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ = 2.32 (3H, s, CH_3); 3.58 (4H, s), 4.50 (2H, s, CH_2–C=N), 6.91 (1H, t, *J* = 7.3 Hz), 6.96 (2H, d, *J* = 8.1 Hz), 7.02 (2H, d, *J* = 8.1 Hz), 7.12 (2H, d, *J* = 8.0 Hz), 7.24 (2H, m); Anal. calcd. for $C_{17}H_{19}N_3$: C, 76.95; H, 7.22; N, 15.84. Found: C, 76.86; H, 7.26; N, 15.89.

N-(4,5-Dihydro-1H-2-imidazolylmethyl)-N-4-hydroxyphenyl-N-phenylamine **3d**: White solid: m.p. 167 °C (Lit.[11] m.p. 166–170 °C); IR (oil film): 3250 (N–H str.) cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz): δ = 3.50 (4H, s), 3.80 (3H, s, OCH_3); 4.50 (2H, s, CH_2–C=N), 5.50 (1H, br s, OH), 6.66–7.30 (9H, m, Ar–H); Anal. calcd. for $C_{16}H_{17}N_3O$: C, 71.89; H, 6.41; N, 15.72. Found: C, 71.97; H, 6.38; N, 12.69.

N-(4,5-Dihydro-1H-2-imidazolylmethyl)-N-3-methylphenyl-N-phenylamine **3e**: White solid: m.p. 104 °C; IR (KBr): 3300 (N–H str.) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ = 2.34 (3H, s, CH_3); 3.58 (4H, s), 4.58 (2H, s, CH_2–C=N), 6.81–6.89 (3H, m), 6.94–7.04 (3H, m), 7.14–7.28 (3H, m); Anal. calcd. for $C_{17}H_{19}N_3$: C, 76.95; H, 7.22; N, 15.84. Found: C, 77.03; H, 7.18; N, 15.80.

N-(4,5-Dihydro-1H-2-imidazolylmethyl)-N-2-methoxyphenyl-N-phenylamine **3f**: Colourless oil; IR (oil film): 3270 (N–H str.) cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz): δ = 3.50 (4H, s), 3.77 (3H, s, OCH_3); 4.45 (2H, s, CH_2–C=N), 6.66-7.30 (9H, m, Ar–H); Anal. calcd. for $C_{18}H_{19}N_3O$: C, 72.57; H, 6.81; N, 14.93. Found: C, 72.49; H, 6.85; N, 14.95.

N-(4,5-Dihydro-1H-2-imidazolylmethyl)-N-3-hydroxyphenyl-N-phenyl amine **3g**: Colourless oil; IR (oil film): 3250 (N–H str.) cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz): δ = 3.50 (4H, s), 4.45 (2H, s, CH_2–C=N), 5.49 (1H, br s, OH); 6.66–7.30 (9H, m, Ar–H); Anal. calcd. for $C_{16}H_{17}N_3O$: C, 71.89; H, 6.41; N, 15.72. Found: C, 72.00; H, 6.37; N, 12.67.

N-(4,5-Dihydro-1H-2-imidazolylmethyl)-N-3-hydroxyphenyl-N-4-methylphenyl amine **3h**: White solid: m.p. 174 °C (Lit.[12] m.p. 174–175 °C); IR (oil film): 3330 (N–H str.) cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz): δ = 2.36 (3H, s, CH_3), 3.50 (4H, s), 4.50 (2H, s, CH_2–C=N), 5.65 (1H, br s, OH); 6.66–7.25 (8H, m, Ar–H); Anal. calcd. for $C_{17}H_{19}N_3O$: C, 72.57; H, 6.81; N, 14.93. Found: C, 72.68; H, 6.78; N, 14.89.

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References

1 Ciba Ltd., *Swiss patent* 262,433; (*Chem. Abstr*. 1951, **45**, 4746g).
2 W. Saari, W. Halczenko, W. Randall and V. Lotti, *J. Med. Chem.* 1983, **26**, 1769.
3 H. Isler, H. Schellenberg and E. Urech, *US Patent* 2,503,059 (*Chem. Abstr*. 1950, **44**, 6889c).
4 Ciba Ltd., *British patent* 656,472 (*Chem. Abstr*. 1952, **46**, 11248f).
5 H. Normant, *Angew. Chem. Int. Ed. Engl*. 1967, **6**, 1046.
6 J.C. Corbel, P. Uriac, J. Huet, C.A.E. Martin and C. Advenier, *Eur. J. Med. Chem*. 1995, **30**, 3.
7 E.E. Korshin, L.I. Sabirova, A.G. Akhadullin and Y.A. Levin, *Russian Chem. Bull*. 1994, **43**, 431.
8 Ciba Ltd., *Swiss patent* 284,620 (*Chem. Abstr*. 1956, **50**, 5767e).
9 Soc. pour 1'ind.chim. â Bâle. *Swiss patent* 234,985 (*Chem. Abstr*. 1949, **43**, 6240e).
10 E. Urech, A. Marxer, and K. Miescher, *Helv. Chim. Acta*. 1950, **33**, 1386.
11 Ciba Ltd., *Swiss patent* 293,626 (*Chem. Abstr*. 1955, **49**, 14035h).
12 Ciba Ltd., *Swiss patent* 293,627 (*Chem. Abstr*. 1955, **49**, 14035g).