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PREPARATION OF N-SUBSTITUTED AMIDINES†

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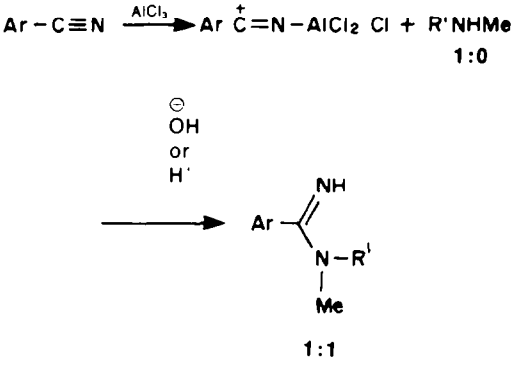
Abstract—N-substituted amidines can be prepared in good yield by heating equimolecular quantities of aryl nitriles and primary amines with $AlCl_3$. Also when a nitrile is kept at room temperature in contact with hydrogen chloride gas in dry ether in the presence of arylamine, amidines may be formed in good yields.

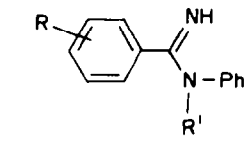
N-Arylamidines have been observed to exhibit high selective activity *in vitro* against *Mycobacterium tuberculosis*.[1] Since relatively few methods are available for the preparation of these compounds in good yield, free from NN'-diarylamidines, the reaction of arylamines with nitriles in the presence of aluminium chloride was examined.

This method involves the interaction between arylamine with a nitrilium ion (**1 : 0** formed by reaction of benzonitrile and aluminium chloride at temperatures between 160–210° to give **1 : 1**. Thus using the appropriate

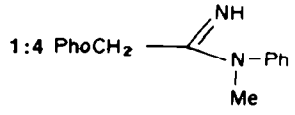


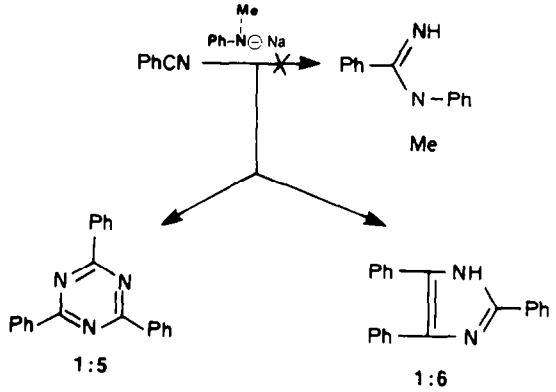
amine and benzonitrile the following *N*-substituted amidines were prepared. With aromatic nitriles, the yield was good (30–80%) but with phenoxyacetonitrile the yield was only 18%.

In an attempted alternative procedure, the amine was converted into stronger nucleophile (sodio-methyaniline) prior to the addition of the nitrile but it merely caused trimerisation of the nitrile to 2,4,6-triazine **1 : 5**, kyaphenine **1 : 5**, and 2,4,5-triphenyl imidazole, lophine **1 : 6**.



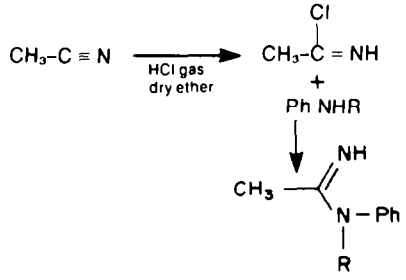
1 : 2 R = H, R' = Et
1 : 3 R = p-CH_3, R' = Me





Successful amidine synthesis using sodio derivatives of primary arylamines and benzonitrile have been reported by Cooper and Partridge[1] but even in this case 2,4,5-tri-phenylimidazole, lophine **1 : 6** was isolated.

Although imidoyl chlorides are recognised intermediates in amidine synthesis, those derived from primary amides are not stable and loose hydrogen chloride gas to generate a nitrile.[4] However, when a nitrile is kept at room temperature in contact with hydrogen chloride gas in dry ether and in the presence of arylamine, amidines may be formed in good yields; presumably the amine reacts with the low concentration of imidoyl chloride formed *in situ*; it is unlikely that such a reaction relies on simple protonation as a means of generating a reactive nitrilium ion since when these are normally encountered, they feature in reactions at elevated temperatures. This reaction is limited to amines not more basic than pKa of about 5, since a moderate concentration of free amine is required as a nucleophile.



The following amidines were prepared using the above method: R = Me; R = Et; R = Bu; R = $ClCH_2C(=NH)NMePh, HCl$. The oily amidines were characterised as the picrates or hydrochlorides as the

distilled bases gave unsatisfactory elemental analysis data. All the NN-disubstituted amidines prepared showed the presence of (NH) in IR (ν_{max} 3300–3500 cm^{-1}) and an exchangeable broad proton signal in NMR (δ 5.40–10.22).

When *N*-methyl-*N*-phenylchloroacetamidinium hydrochloride **2:0** was stored over calcium chloride it decomposed to give a water insoluble product, dichlorodiacetamide ($ClCH_2CONHCOCH_2Cl$) which was also prepared unambigouusly by the method of Tröger and Lüning.[2] The IR showed characteristic absorption at ν_{max} 3280 and 1760 cm^{-1} for (NH) and (CONHCO) respectively. The NMR spectrum exhibited the two methylene groups as a singlet at δ 4.43 and the (NH) function resonated as a broad signal at δ 11.33.

EXPERIMENTAL

Spectra were obtained using Perkin Elmer 257 IR spectrophotometer for thin films or KBr discs, a Varian E.M.-360 NMR spectrometer operating at 60 MHz in $CDCl_3$ (tretramethylsilane was the internal reference).

All organic extracts were dried with anhydrous magnesium sulphate. Microanalyses were determined by Mr. T. J. Spencer, Department of Chemistry, University of Nottingham. NMR spectra were measured by Dr. S. R. Chhabra, Department of Pharmacy, University of Nottingham, U.K.

N-Ethyl-N-phenylbenzamidine (**1 : 2**)

A mixture of redistilled benzonitrile (0.5 mole) and redistilled *N*-ethyl aniline (0.5 mole) was treated with anhydrous aluminium chloride (67.0 g, 0.55 mole) portionwise with thorough stirring and during 30 min the exothermic reaction was moderated by occasional external cooling. The suspension was then heated at 160° for 20 min and while still molten, was poured slowly into a thoroughly stirred mixture of concentrated hydrochloric acid (16.0 ml) and water (1200 ml). After the addition of charcoal, the suspension was stirred while being externally cooled and then filtered through Kieselguhr. The filtrate was poured in a steady stream into a stirred solution of sodium hydroxide (170 g) in water (1000 ml); extracted with chloroform, dried and evaporated to furnish *N*-ethyl-*N*-phenylbenzamidine, a colourless viscous oil with b.p. 170–172° at 0.2 mmHg. The NMR spectrum showed signals at s, 1.21, t, 3H(CH_2CH_3) J_{CH_3,CH_2} 8 Hz; 4.0, q, 2H(CH_2–CH_3) J_{CH_2,CH_3} 8 Hz; 6.62, b, 1H(NH); 6.72–7.56, m, 10H (Aromatic protons). The IR spectrum showed characteristic absorptions at 3300 (NH) and 1620 cm^{-1} for (C : N). The amidine **1 : 2** was charaterised as its picrate which crystallised from ethanol as yellow prisms, m.p. 203–204°. Found C, 55.5, H, 4.5; N, 15.3; $C_{21}H_{19}N_5O_7$ requires C, 55.6, H, 4.2; N, 15.4%.

N-Methyl-N-phenyl-p-toluamidine (**1 : 3**)

This amidine b.p. 181–183° at 0.2 mmHg was prepared from p-tolunitrile (11.7 g, 0.1 mole), *N*-methylaniline (10.7 g, 0.1 mole) and aluminium chloride (14.0 g, 0.1 mole) in 62% yield, as described for amidine **1 : 2**. The IR and NMR spectra of the amidine showed signals at 3300 (NH), 1580 cm^{-1}, CN and δ 2.24, S, 3H(CH_3); 3.44, S, 3H(N–CH_3); 6.40, b, 1H(NH); 6.76–7.21, m, 9H (aromatic protons). Its picrate formed yellow prisms, m.p. 198–200° from ethanol. Found C, 55.3; H, 4.5; N, 14.8; $C_{21}H_{19}N_5O_7$ requires C, 55.6; H, 4.2; N, 15.4%.

N-Methyl-N-phenoxyacetamidine (**1 : 4**)

A mixture of phenoxyacetonitrile[3] (13.39, 0.1 mole) and redistilled *N*-methylaniline (5.3 g, 0.05 mole) cooled to 0°, was saturated with dry hydrogen chloride gas. The mixture was initially kept at 5° for three days and then at room temp. for three weeks. Excess of solvent was evaporated from the resulting suspension and the product dissolved in water, basified with 2*N*-sodium hydroxide, extracted with chloroform, dried and evaporated to furnish *N*-methyl-*N*-phenylphenoxy acetamidine (6.97 g, 61%).

This amidine was also prepared by a procedure similar to that described for *N*-ethyl-*N*-phenylbenzamidine from *N*-methylaniline, phenoxyacetonitrile and aluminium chloride in 18% yield. The IR showed 3200, (NH), 1640 cm^{-1} (C : N); NMR δ 3.52, S, 3H(NCH_3); 4.99, S, 2H(OCH_2); 6.69–7.75, m, 10H (aromatic protons) 10.09, b, 1H(NH). Its hydrochloride crystallised as colourless plates, m.p. 246–247°, from methanol-ether. Found C, 64.8; H, 6.1; N, 9.9; $C_{15}H_{17}ClN_2O$ requires C, 65.0; H, 6.2; N, 10.1%.

N-Methyl-N-phenylacetamidine (**1 : 7**)

This amidine was prepared in 56% yield as a colourless oil, b.p. 92–94° at 0.2 mmHg, by interaction of redistilled *N*-methylaniline (0.1 mole) and acetonitrile (0.05 mole) in ether saturated with dry hydrogen chloride gas as described for *N*-methyl-*N*-phenylphenoxyacetamidine. The IR spectrum showed signals at 3300 (NH); 1620 cm^{-1} (C : N) and the NMR spectrum had the following characteristic absorptions δ 1.83, S, 3H(CH_3); 3.20, S, 3H(NCH_3); 5.40, b, 1H(NH); 6.94–7.49, m, 5H(aromatic protons). Its picrate was crystallised from toluene as yellow prisms, m.p. 141–142°. Found C, 47.4; H, 4.3; N, 18.2; $C_{15}N_{15}N_5O_7$ requires C, 47.7; H, 4.0; N, 18.5%.

N-Ethyl-N-phenylacetamidine (**1 : 8**)

Prepared (15.9 g, 97%, b.p. 128–130° at 0.25 mmHg) from acetontrile (8.2 g, 0.2 mole), *N*-ethylaniline (12.2 g, 0.1 mole) and hydrogen chloride gas in the usual way, as a colourless oil. IR and NMR spectra had the following signals 3300 (NH); 1620 cm^{-1} (C : N) and δ 1.12, t, 3H(CH_2–CH_3) J_{CH_3,CH_2} 8 Hz; 1.79, S, 3H(CH_3); 3.72, q, 2H(CH_2, CH_3) J_{CH_2,CH_3} 8 Hz; 6.13, b, 1H(NH); 7.00–7.46, m, 5H (aromatic protons). Its picrate separated as yellow prisms, m.p. 119–120° from toluene. Found C, 49.0; H, 4.5; N, 17.6; $C_{16}H_{17}N_5O_7$ requires C, 49.1; H, 4.3; N, 17.9%.

N-n-Butyl-N-phenylacetamidine (**1 : 9**)

This amidine was prepared from acetonitrile (8.2 g, 0.2 mole) n-butylaniline (14.92 g, 0.1 mole) and hydrogen gas in 98% (18.8 g) yield, as a colourless oil with b.p. 136–138° at 0.2 mmHg. The IR and NMR spectra showed the following characteristic signals at 3300 (NH) and 1600 cm^{-1} (C : N) δ 0.62–1.69, m, 7H($NCH_2(CH_2)_2CH_3$); 1.85, S, 3H(CH_3–C); 3.36, t, 2H(NCH_2)($CH_2)_2CH_3$) J_{NCH_2,CH_2} 8 Hz; 5.95, s, 1H(NH); 6.90–7.53, m, 5H (aromatic protons). The amidine was characterised as its picrate which crystallised from toluene as yellow prisms, m.p. 116–117.5°. Found C, 51.2; H, 5.3; N, 16.5; $C_{18}H_{21}N_5O_7$ requires C, 51.5; H, 5.0; N, 16.7%.

N-Methyl-N-phenylchloroacetamidinium hydrochloride (**2 : 0**)

This very hygroscopic hydrochloride was prepared in 71% yield from chloroacetonitrile (0.2 mole), N-methylaniline (0.1 mole) and hydrogen chloride in the usual way. The NMR spectrum in DMSo-d6 had the following absorptions at δ 3.45, s, 3H(NCH_3); 4.35, s, 2H(CH_2); 7.49, s. 5H (aromatic protons) 10.22, b, 2H(NH_2^+). It was characterised as its picrate yellow prisms, m.p. 162–163° from ethanol. Found C, 43.6; H, 3.6; N, 16.6; $C_{15}H_{14}ClN_5O_7$ requires C, 43.7; H, 3.4; N, 17.0% *M* (poténtiometric titration) 411.6 *M* for formula $C_{15}H_{14}ClN_5O_7$. Storage of the hydrochloride over calcium chloride gave the water insoluble dichlorodiacetamide, m.p. 196° (alone or admixture with an authentic sample[2]) (see below).

An unequivocal synthesis of dichlorodiacetamide

This compound was prepared according to the method of Tröger and Lüning.[2] An intimate mixture of chloroacetonitrile (0.75 g, 0.01 mole) and chloroacetic acid (0.94 g, 0.01 mole) was heated at 142° in a sealed tube for 4 hr. The grey product (30%) m.p. 195–196° (lit.[2] m.p. 195°) was crystallised from acetone as colourless needles of unchanged melting point.

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