A Novel Synthesis of *N*-(2-Alkynyl)arylamines

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A new general one-pot method for the high yield synthesis of secondary *N*-(2-alkynyl)arylamines by reaction of *N*-(methoxymethyl)arylamines and 1-alkynyllithium is described. This procedure has successfully been extended to the preparation of symmetrically and non-symmetrically substituted 2-butyne-1,4-diamines.

Propargylamines are an important group of compounds due to the biological activity of some of them,[1] and also to their interest as starting materials in several chemical transformations.[2] The cyclization processes, useful for the synthesis of heterocycles,[3] and the rearrangement of secondary amines

giving azabutadienes[4] or aminobutadienes,[5] are two of the most remarkable reactions of these substrates. The synthesis of propargylamines has been principally achieved by the reaction of propargylic halides and amines,[2,6,7] but low yields and the presence of polyalkylated products were reported. Another approach to the preparation of these compounds is the Mannich reaction of acetylenes,[8] but this process normally does not work with aromatic amines, particularly for the primary ones. Although the greater number of therapeutically important propargylic amines contain an aromatic ring in their molecular

Table. *N*-(2-Alkynyl)arylamines **5** Prepared

Product	Yield[a] (%)	bp (°C)/Torr	Molecular Formula[b] or Lit. bp (°C)/Torr	^{1}H-NMR ($CDCl_3$/TMS)[c] δ, J(Hz)	^{13}C-NMR ($CDCl_3$)[c] δ[d]	MS (70 eV)[e] *m/z* (%)
5a	90	46/0.1	118–112/12[7]	2.1 (t, 1H, J = 2.7, CH); 3.6 (s, 1H, NH); 3.9 (d, 2H, J = 2.7, CH_2); 6.4–7.3 (m, 5H, H_{arom})	33.8 (t); 72.7 (d); 82.7 (d); 114.3 (d); 119.2 (d); 130.3 (d); 148.4 (s)	131 (M^+, 55); 130 ($C_9H_8N^+$, 100); 92 ($C_6H_6N^+$, 100); 77 ($C_6H_5^+$, 17); 65 ($C_5H_5^+$, 18)
5b	97	122/0.1	$C_{15}N_{21}N$ (215.3)	0.9 (br t, 3H, CH_3); 1.1–1.6 (m, 8H, $(CH_2)_4$); 2.1 (br t, 2H, $\equiv C-CH_2-C$); 3.7 (br s, 1H, NH); 3.7 (s, 2H, $\equiv C-CH_2-N$); 6.3–7.2 (m, 5H, H_{arom})	14.1 (q); 18.8 (t); 22.7 (t); 28.6 (t); 28.9 (t); 31.5 (t); 33.8 (t); 78.0 (s); 83.6 (s); 113.7 (d); 118.2 (d); 129.4 (d); 148.6 (s)	215 (M^+, 58); 214 ($M^+ - 1$), 100); 144 ($C_{10}H_{10}N^+$, 58); 130 ($C_9H_8N^+$, 60); 106 ($PhNHCH_2^+$, 27); 93 ($C_6H_7N^+$, 77)
5c	90	81/0.1	$C_{12}H_{13}N$ (171.2)	1.8 (s, 3H, CH_3); 3.6 (br s, 1H, NH); 4.0 (s, 2H, $CH_2-C\equiv$); 5.2 (m, 2H, $C=CH_2$); 6.6–7.3 (m, 5H, H_{arom})	23.3 (q); 34.0 (t); 84.8 (s); 86.9 (s); 113.6 (d); 118.7 (d); 122.2 (t); 127.1 (s); 129.4 (d); 148.5 (s)	171 (M^+, 71); 170 (($M^+ - 1$), 63); 154 (($M^+ - NH_3$)$^+$, 21); 130 ($C_9H_8N^+$, 34); 106 ($PhNHCH_2^+$, 21); 77 ($C_6H_5^+$, 100)
5d	95	113/0.1	206/15[13]	3.9 (s, 2H, CH_2); 4.5 (s, 1H, NH); 6.4–7.3 (m, 10H, H_{arom})	34.0 (t); 83.9 (s); 88.0 (s); 11.2 (d); 118.9 (d); 123.7 (s); 129.0 (d); 129.0 (d); 129.9 (d); 132.3 (d); 147.9 (s)	207 (M^+, 45); 206 (($M^+ - 1$), 49); 130 ($C_9H_8N^+$, 8); 115 ($C_9H_7^+$, 100); 77 ($C_6H_5^+$, 11)
5e	97	121/0.1	$C_{16}H_{15}N$ (221.3)	2.0 (br s, 1H, NH); 2.1 (s, 3H, CH_3); 3.9 (s, 2H, CH_2); 6.3–7.2 (m, 9H, H_{arom})	21.1 (q); 34.0 (t); 83.2 (s); 87.3 (s); 111.0 (d); 114.9 (d); 119.6 (d); 123.2 (s); 128.8 (d); 128.8 (d); 129.7 (d); 132.1 (d); 139.5 (s); 148.8 (s)	221 (M^+, 47); 220 (($M^+ - 1$), 49); 144 ($C_{10}H_{10}N^+$, 21); 130 ($C_9H_8N^+$, 13); 115 ($C_9H_7^+$, 100)
5f	90	oil	$C_{10}H_{11}NO$ (161.2)	3.1–3.8 (br s, 2H, NH, OH); 3.8 (s, 2H, CH_2N); 4.1 (s, 2H, CH_2O); 6.4–7.3 (m, 5H, H_{arom})	34.6 (t); 51.3 (t); 82.5 (s); 83.5 (s); 114.5 (d); 119.3 (d); 130.1 (d); 148.0 (s)	161 (M^+, 95); 160 (($M^+ - 1$), 45); 144 ($C_{10}H_{10}N^+$, 58); 130 ($C_9H_8N^+$, 85); 115 ($C_9H_7^+$, 44); 93 ($C_6H_7N^+$, 55); 77 ($C_6H_5^+$, 100)
5g	95	oil	$C_{13}H_{15}NO$ (201.3)	1.7 (s, 3H, CH_3); 2.7–3.0 (br s, 2H, NH, OH); 3.9 (s, 2H, CH_2N); 4.1 (d, 2H, J = 6.2, CH_2O); 5.8 (t, 1H, J = 6.2, C=CH); 6.5–7.2 (m, 5H, H_{arom})	16.9 (q); 33.8 (t); 58.3 (t); 84.2 (s); 85.1 (s); 113.6 (d); 118.7 (d); 119.9 (s); 129.6 (d); 136.3 (d); 147.7 (s)	201 (M^+, 15); 182 ($C_{13}H_{12}N^+$, 70); 168 ($C_{12}H_{10}N^+$, 37); 118 ($C_8H_8N^+$, 41); 106 ($PhNHCH_2^+$, 44); 93 ($C_6H_8N^+$, 90); 77 ($C_6H_5^+$, 100)
5h	88	oil	$C_{14}H_{20}N_2$ (216.3)	0.9 (t, 6H, J = 8.0, CH_3); 2.4 (q, 4H, J = 8.0, CH_3CH_2N); 3.3 (s, 2H, CH_2NEt_2); 3.7–3.9 (br s, 1H, NH); 3.9 (s, 2H, $\equiv C-CH_2NH$); 6.7–7.3 (m, 5H, H_{arom})	12.0 (q); 33.0 (t); 40.3 (t); 46.8 (t); 77.9 (s); 82.2 (s); 113.4 (d); 117.8 (d); 129.1 (d); 148.0 (s)	216 (M^+, 48); 201 (($M^+ - CH_3$), 100); 144 ($C_{10}H_{10}N^+$, 88); 143 ($C_{10}H_9N^+$, 92); 123 ($C_8H_{13}N^+$, 43); 115 ($C_9H_7^+$, 37)
5i	90	oil	$C_{15}H_{22}N_2$ (230.4)	1.1 (t, 6H, J = 7.5, CH_3CH_2); 2.3 (s, 3H, CH_3-Ar); 2.6 (q, 4H, J = 7.5, CH_3CH_2N); 3.4 (d, 2H, CH_2NEt); 3.4–3.6 (br s, 1H, NH); 4.0 (s, 2H, CH_2NHAr); 6.5–7.4 (m, 4H, H_{arom})	12.8 (q); 21.7 (q); 33.8 (t); 40.0 (t); 57.4 (t); 78.1 (s); 83.0 (s); 110.2 (d); 114.8 (d); 119.1 (d); 129.4 (d); 138.9 (s); 148.6 (s)	230 (M^+, 39); 215 (($M^+ - CH_3$), 54); 158 (($M^+ - C_4H_{10}N$), 34); 143 ($C_{10}H_9N^+$, 100); 123 ($C_8H_{13}N^+$, 31)
5j	97	oil	$C_{16}H_{16}N_2$ (236.3)	3.2–3.5 (br s, 2H, 2NH); 3.9 (s, 4H, $CH_2C\equiv CCH_2$); 7.4–6.6 (m, 10H, H_{arom})	34.3 (t); 80.9 (s); 114.1 (d); 118.9 (d); 129.8 (d); 147.7 (s)	236 (M^+, 73); 235 (($M^+ - 1$), 69); 144 ($C_{10}H_{10}N^+$, 37); 143 ($C_{10}H_9N^+$, 100); 130 ($C_9H_8N^+$, 36); 115 ($C_9H_7N^+$, 62); 106 ($PhNHCH_2^+$, 50)
5k	95	oil	$C_{17}H_{18}N_2$ (250.3)	2.2 (s, 3H, CH_3); 3.3–3.5 (br s, 2H, 2NH); 3.9 (s, 4H, $CH_2C=CCH_2$); 6.5–7.4 (m, 9H, H_{arom})	21.1 (q); 33.1 (t); 33.3 (t); 80.0 (s); 80.2 (s); 110.2 (d); 113.3 (d); 114.1 (d); 118.0 (d); 119.0 (s); 129.4 (d); 129.4 (d); 138.9 (s); 147.8 (s); 147.8 (s)	250 (M^+, 94); 249 (($M^+ - 1$), 78); 156 ($C_{11}H_{10}N^+$, 58); 143 ($C_{10}H_9N^+$, 100); 115 ($C_9H_7^+$, 52); 106 ($PhNHCH_2^+$, 44); 77 ($C_6H_5^+$, 67)

[a] Based on starting *N*-(methoxymethyl)arylamine **3**.

[b] Satisfactory microanalyses obtained: C ±0.36, H ±0.13, N ±0.15; except: **5g** (C +0.42).

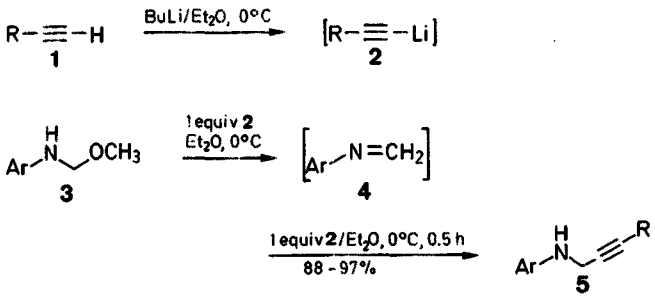
[c] Recorded on a Varian FT-80A and a Bruker AC-300 spectrometers.

[d] With reference to the solvent as internal standard.

[e] Obtained on a Hewlett-Packard 5987A spectrometer.

structure (for instance, pargyline, deprenyl, clorgyline)[1] it is possible to say that there are no simple synthetic methods for the preparation of these compounds allowing to modify the acetylenic and the aromatic moieties.

We report here an easy synthesis of *N*-(2-alkynyl)arylamines **5** based on the reactivity of the recently by us prepared monomeric methyleneamines **4**[9] with nucleophiles. The unstable products **4** are easily accessible using their precursors *N*-(methoxymethyl)-arylamines **3**.[10] We have found that 1-alkynyllithium (prepared *in situ* from butyllithium and the corresponding alkyne) react with **4** (liberated from **3** by basic treatment with **2**) in ether at 0 °C to afford *N*-(2-alkynyl)arylamines **5** in almost quantitative yields in a clean process (Table).



5	R	Ar
a	H	Ph
b	n-C_6H_{13}	Ph
c	CH_2=CCH_3	Ph
d	Ph	Ph
e	Ph	3-$CH_3C_6H_4$
f	CH_2OH	Ph
g	CH_3C=$CHCH_2OH$	Ph
h	CH_2NEt_2	Ph
i	CH_2NEt_2	3-$CH_3C_6H_4$
j	CH_2NHPh	Ph
k	CH_2NHPh	3-$CH_3C_6H_4$

The reaction requires two equivalents of **2**, the first producing the imine **4**, and the second reacting with **4**. When only one equivalent is used, a small amount of **5** is formed. The 1,3,5-triarylhexahydro-1,3,5-triazine (Ar–N=CH_2)$_3$, corresponding to the trimerization of **4**, is obtained as main product.

An ethereal suspension of dilithium acetylide prepared by one often conventional methods[11] is the starting material for the synthesis of **5a**. If propargylaniline **5a** is used as starting alkyne the preparation of aromatic symmetrical **5j** or aromatic unsymmetrical diamines **5k** is easily achieved. On the other hand, aliphatic-aromatic unsymmetrical diamines **5h**, **5i** are obtained by the use of commercially available *N*,*N*-diethylpropargylamine.

Compounds **5** can also be prepared starting on the isolated methyleneamines **4**[9] by direct reaction with one equivalent of **2** at – 60 °C. This procedure gives lower yields of **5** and requires a greater experimental complexity than the method described in this communication.

All compounds were fully characterized by their ^{1}H-, ^{13}C-NMR, and MS spectra (Table). Data for known compounds were found to be in good agreement with those reported in the literature.

The general one-pot method reported herein for the synthesis of compounds **5** gives much better yields than those in the literature[6,7] when applied to simple alkynes and allows the preparation of new *N*-(2-alkynyl)arylamines with functionalized chain R and starting from commercial alkynes. This procedure makes feasible to obtain symmetrical and unsymmetrical 2-butyne-1,4-diamines, which are an almost unknown class of compounds[12] offering interesting synthetical possibilities. For the above reasons it could become the method of choice for *N*-(2-alkynyl)arylamines.

N-(2-Alkynyl)arylamines 5; General Procedure:
In a dried, argon-filled Schlenk tube, fitted with stirrer and addition funnel, the alkyne **1** (10 mmol) is dissolved in dry Et_2O (25 mL). A solution of BuLi (4 mL, 10 mmol, 2.5 N in hexane)[14] in Et_2O (10 mL) is added slowly at 0 °C, followed by the corresponding *N*-(methoxymethyl)arylamine **3** (5 mmol). The solution is stirred at 0 °C for 0.5 h, then quenched with H_2O (100 mL). The mixture is extracted with Et_2O (2 × 25 mL), and the organic phase is dried (Na_2SO_4). The solvent and the excess of **1** are removed under vacuum to yield the corresponding **5** as residue (GC purity of the crude product > 90%). Compounds **5** are purified by distillation under vacuum.

This work was supported by the Comisión Asesora de Investigación Científica y Técnica (CAICYT Project N° 0876/84). One of us (G.C.) is grateful to the Ministerio de Educación y Ciencia for a fellowship.

Received: 12 July 1988; revised: 16 September 1988

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(14) A suspension of dilithium acetylide[11] (15 mmol in ether) is used in the preparation of **5a**. When the starting acetylene **1** has acidic hydrogens, twice amount of butyllithium (8 mL, 20 mmol) is added (**5f**, **5g**, **5j**, **5k**).