A New General Method for the Synthesis of Tertiary Propargylamines (*N,N*-Dialkyl-2-alkynamines)[1]

Alan R. Katritzky,* John K. Gallos,[2] Konstantina Yannakopoulou

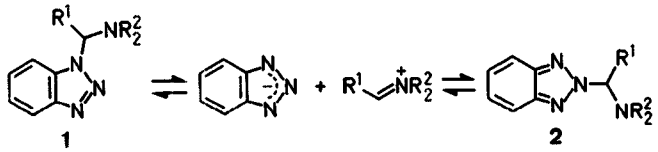
Department of Chemistry, University of Florida, Gainesville, FL 32611, USA

A new method has been developed for the preparation of propargylamines, compounds of pharmaceutical interest. The method employs mild conditions, affords good overall yields, and is successfully applied even in cases where other methods fail.

Tertiary propargylamines (*N,N*-dialkyl-2-alkynamines) constitute a class of compounds with great pharmaceutical interest. A plethora of recent references reflects their increasing importance in a variety of biological systems.[3-7] For instance, *N,N*-disubstituted 1-aryl-3-aminopropynes exhibit[5] antiulceration, sedative, and antispasmodic effects on smooth muscles, and analgesic-antiinflammatory properties; *N*-methyl-*N*-propargylbenzylamine shows aldehyde dehydrogenase inhibitory activity;[6] finally, compounds possessing the 1,3-enyne structure are biologically active analogues of the important antimycotic terbinafine.[7]

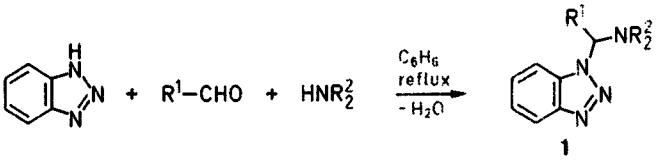
A number of methods exists for the preparation of tertiary propargylamines. Mannich reactions of an arylacetylene with formaldehyde and a secondary amine[8] [sometimes with a catalytic amount of copper(II) acetate and copper(I) chloride or iodide[5,9,10]] give good yields, but are restricted to compounds in which the triple bond and N-atom are connected by a methylene group. Aryl iodides couple with copper acetylenides[10] to afford propargyl alcohols which are then converted to propargylamines in two additional steps. Reactions of propargyl bromide with secondary amines afford 3-unsubstituted propargylamines.[11-13] 2-Amino-3-alkynols have been prepared from preformed propargylamines by lithiation and subsequent reaction with carbonyl compounds.[14] According to a recent publication,[15] aminals react with phenylacetylene in the presence of copper(I) halides to give 3-substituted propargylamines. The scope of this reaction is, however, restricted to 3-aryl substituents.[16] 3-Substituted propargylamines are also produced in base-catalyzed rearrangements of allyl propynyl cations,[17] reactions which are of great mechanistic and theoretical, but limited synthetic, interest.

We now report a new general method for the synthesis of both simple tertiary propargylamines and of 3-aryl- or alkyl-substituted tertiary propargylamines. This method is based on the ability of 1-(dialkylaminomethyl)benzotriazoles **1** to react with alkyl- and arylmagnesium halides to produce amines or amides in good to excellent yields.[18-20] The carbon atom of the methine group in **1** possesses enhanced electrophilicity probably due to the existence[21] of a mobile equilibrium between the two isomers **1** and **2** via the benzotriazolide – iminium ion pair.



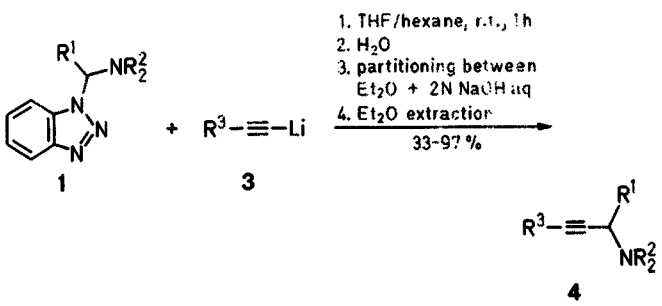
1 **2**

1-(Dialkylaminomethyl)benzotriazoles **1** (R^1 = H) are readily available in almost quantitative yields by reaction of benzotriazole, formaldehyde, and the appropriate secondary amine.[19,21] The corresponding 1-(1-dialkylaminoalkyl)benzotriazoles **1** ($R^1 \neq$ H) can be prepared if another aldehyde is used instead of formaldehyde.[18] These latter compounds, prepared in benzene by azeotropic distillation of the water produced, need not be isolated: the benzene solutions can be directly used for the next step.



1

We now report that adducts **1**, either as isolated compounds or as benzene solutions, react at 20 °C with an equimolecular amount of 1-alkyne lithium salt **3**, prepared *in situ* by reaction of 1-alkynes, alkyl or arylacetylenes with butyllithium, to give high yields of the propargylamines **4** in an essentially one-pot procedure.



1 **3** **4**

Satisfactory purity was achieved by simply washing the reaction mixture with 1 N sodium hydroxide and water, and in some cases passing the resulting oil through a silica gel column (Table 1). Examples **4i–n** (Table 1) demonstrate that starting from an aldehyde, a secondary amine, and an acetylene, the corresponding propargylamine can be obtained in very good overall yield without isolation of the intermediates **1**. Products **4a–g** and **4i** were characterized as their picrate salts (Table 1): except for **4b**, **4c**, and **4f** all are novel compounds. In all cases, comparison of the ^{1}H- and ^{13}C-NMR spectra to those of structurally similar compounds reported in the literature[11,22] aided the complete characterization of the amines.

In summary, our method provides a reaction of wide scope and high yields for the preparation of propargylamines of type **4** with virtually no limitations in the variety of R^1, R^2, or R^3. These 3-substituted propargylamines **4** with $R^1 \neq$ H cannot be prepared by the Mannich reaction, which is limited to formaldehyde, and the starting materials for other routes to **4** are not readily available.

1-(1-Dialkylaminoalkyl)benzotriazoles 1 ($R^1 \neq$ H); General Procedure: Benzotriazole (7.862 g, 66 mmol) is mixed with the appropriate secondary amine (66 mmol) and the aldehyde (66 mmol) (Table 1) in dry benzene (50 mL). The mixture is heated under reflux in a Dean-Stark apparatus until the theoretical amount of H_2O has been collected (≈ 1.2 mL). The water-free benzene solution is used directly for the

reactions with the 1-lithio-1-alkynes **3** (see below). The benzotriazole adducts **1** leading to propargylamines **4d, e** are isolated by removing the benzene under reduced pressure and triturating the resulting oil with Et_2O/petroleum ether (bp 40–60°C) (1:2) while cooling in a dry ice/acetone bath.[18]

Propargylamines 4a–h; General Procedure:

To a cold (−70°C) solution of the 1-alkyne or arylacetylene (5 mmol) (see Table 1 for the specific reagents) in freshly distilled THF (20 mL), a 2.5 molar solution (2.2 mL) of *n*-BuLi (5.5 mmol) in hexane is added under an argon atmosphere. Stirring at room temperature for 2 h is

Table 1. Propargylamines **4** Prepared[a]

Product	NR^2_2	R^1	R^3	Yield (%)	mp (°C)[i] of Picrate	Molecular Formula	^{1}H-NMR ($CDCl_3$/TMS)[j] of Products **4** δ, J(Hz)
4a	$N(CH_2C_6H_5)_2$	H	C_6H_5	76[b]	172–174	$C_{29}H_{24}N_4O_7$[c] (540.5)	3.45 (s, 2H); 3.73 (s, 4H); 7.15–7.35 (m, 9H); 7.35–7.50 (m, 6H)
4b	$N(CH_2CH_2)_2$	H	C_6H_5	73[b]	154–157	$C_{19}H_{18}N_4O_7$[c] (414.4)	1.8 (m, 4H); 2.7 (m, 4H); 3.6 (s, 2H); 7.26 (m, 3H); 7.40 (m, 2H)
4c	$N(CH_3)_2$	H	C_6H_5	79	115–118	$C_{17}H_{16}N_4O_7$[c] (388.3)	2.33 (s, 6H); 3.43 (s, 2H); 7.25 (m, 3H); 7.4 (m, 2H)
4d	$N(CH_2CH_2)_2$	*i*-C_3H_7	C_6H_5	67[b]	116–118	$C_{22}H_{24}N_4O_7$[c] (456.4)	1.05 (d, 3H, J = 7); 1.1 (d, 3H, J = 6); 1.76 (m, 4H); 1.9 (m, 1H); 2.7 (m, 4H); 3.25 (d, 1H, J = 8); 7.2 (m, 3H); 7.4 (m, 2H)
4e	$N(CH_2C_6H_5)_2$	*i*-C_3H_7	C_6H_5	95	130–132	$C_{32}H_{30}N_4O_7$[c] (582.6)	1.03 (d, 3H, J = 7); 1.04 (d, 3H, J = 6); 1.98 (m, 1H); 3.15 (d, 1H, J = 10); 3.48 (d, 2H, J = 14); 3.9 (d, 2H, J = 14); 7.25 (m, 9H); 7.45 (m, 6H)
4f	$N(CH_2CH_2)_2O$	C_6H_5	C_6H_5	33[b,d]	175–177	$C_{25}H_{22}N_4O_8$[c] (506.5)	2.49 (t, 4H, J = 4); 3.58 (t, 4H, J = 4); 4.65 (s, 1H); 7.18 (m, 6H); 7.39 (m, 2H); 7.52 (m, 2H)
4g	$N(CH_2C_6H_5)_2$	*i*-C_3H_7	*n*-C_6H_{13}	96	76–78	$C_{32}H_{38}N_4O_7$[c] (590.7)	0.95 (m, 9H); 1.45 (m, 8H); 1.85 (m, 1H); 2.3 (t, 2H, J = 6); 2.85 (d, 1H, J = 10); 3.35 (d, 2H, J = 14); 3.78 (d, 2H, J = 14); 7.3 (m, 10H)
4h	$N(n\text{-}C_8H_{17})_2$	H	*n*-C_4H_9	90	–	$C_{23}H_{45}N$[e] (335.4)	0.9 (m, 9H); 1.27 (br m, 20H); 1.45 (m, 8H); 2.2 (m, 2H); 2.4 (t, 4H, J = 7); 3.35 (t, 2H, J = 2)
4i	$N(CH_2CH_2)_2CH_2$	C_6H_5	C_6H_5	73[b,f]	157–162[g]	$C_{26}H_{24}N_4O_7$[c] (512.5)	1.43 (m, 2H); 1.57 (m, 4H); 2.55 (br t, 4H); 4.78 (s, 1H); 7.3 (m, 6H); 7.5 (m, 2H); 7.64 (m, 2H)
4j	$N(CH_2CH_2)_2$	*i*-C_3H_7	*n*-C_6H_{13}	71[f]	–	$C_{16}H_{29}N$[e] (235.2)	0.95 (m, 9H); 1.35 (m, 8H); 1.75 (m, 5H); 2.2 (dt, 2H, J = 2, 7); 2.6 (m, 4H); 3.0 (dt, 1H, J = 2, 7)
4k	$N(CH_2CH_2)_2O$	*n*-C_3H_7	C_6H_5	76[f]	–	$C_{16}H_{21}NO$[h] (243.3)	0.97 (t, 3H, J = 7); 1.65 (m, 4H); 2.55 (m, 2H); 2.71 (m, 2H); 3.5 (t, 1H, J = 8); 3.75 (m, 4H); 7.3 (m, 3H); 7.41 (m, 2H)
4l	$N(CH_2CH_2)_2O$	*n*-C_3H_7	*n*-C_6H_{13}	72[f]	–	$C_{16}H_{29}NO$[h] (251.4)	0.9 (m, 6H); 1.4 (m, 12H); 2.21 (dt, 2H, J = 2, 7); 2.49 (m, 2H); 2.62 (m, 2H); 3.25 (dt, 1H, J = 2, 7); 3.7 (m, 4H)
4m	$N(CH_2CH_2)_2O$	*n*-C_7H_{15}	C_6H_5	97[f]	–	$C_{20}H_{29}NO$[h] (299.4)	0.89 (br t, 3H); 1.3 (m, 8H); 1.5 (m, 2H); 1.7 (m, 2H); 2.56 (m, 2H); 2.7 (m, 2H); 3.46 (t, 1H, J = 7); 3.74 (m, 4H); 7.27 (m, 3H); 7.42 (m, 2H)
4n	$N(CH_2CH_2)_2O$	*n*-C_7H_{15}	*n*-C_6H_{13}	81[f]	–	$C_{20}H_{37}NO$[e] (307.3)	0.9 (m, 6H); 1.3 (br m, 22H); 2.2 (dt, 2H, J = 2, 7); 2.5 (m, 2H); 2.62 (m, 2H); 3.23 (dt, 1H, J = 2, 7); 3.73 (m, 4H)

[a] Details for the preparation and characterization of benzotriazole adducts **1b** and **1c** are presented in Ref. 21; for adducts **1a, h** Ref. 18; adducts **1d–g** Ref. 18. Adducts **1i–n** were not isolated and the reactions were carried out in a one-pot procedure.

[b] Yields refer to the product obtained by passing the crude oil through a silica gel column (230–400 mesh) eluted with the following: Compounds **4a, 4d,** and **4i** CH_2Cl_2, compound **4b** EtOAc/CH_2Cl_2, and compound **4f** hexane/CH_2Cl_2.

[c] Picrates. The microanalyses showed the following maximum deviations from the calculated values: C ±0.37, H ±0.40, N ±0.35.

[d] Benzylidenacetophenone was obtained as the main product in 50% yield.

[e] The amine decomposed on vacuum distillation and the picrate did not crystallize, therefore the exact mass (M^+) was determined; maximum deviation: ±0.0020 (±6.6 ppm).

[f] Overall yield based on starting secondary amine. Reactions without isolation of the intermediate 1-(1-dialkylaminoalkyl)benzotriazoles **1** ($R^1 \neq H$).

[g] The amine has mp 52–55°C (Lit.[15] mp 52–53°C).

[h] The amine decomposed on vacuum distillation and the picrate did not crystallize. Analytically pure samples were prepared by passing the amine through a small column of silica gel packed in hexane and using hexane/Et_2O (in ratios of increasing polarity) as eluent. Maximum deviations from the calculated values: C ±0.15, H ±0.04, N ±0.05.

[i] Uncorrected, measured on a hot stage microscope.

[j] Obtained on a Varian XL-200 spectrometer.

Table 2. ^{13}C-NMR-Spectral Data of Propargylamines **4** [δ($CDCl_3$)]

Compound	R^3	$-C\equiv C-$	$CH-$	R^1	$-NR_2^2$
4a	123.3; 127.9; 128.2; 131.7	84.4; 85.8	41.9		57.6; 127.0; 128.2; 128.9; 138.8
4b[a]	123.1; 127.7; 128.0; 131.5	84.2; 85.1	43.6		23.6; 52.4
4c	122.9; 127.6; 127.8; 131.3	84.2; 84.9	48.1		43.8
4d	123.6; 127.6; 128.0; 131.6	85.6; 87.6	62.3	19.4; 20.1; 31.9	23.5; 50.1
4e	123.7; 127.8; 128.2; 131.8	86.2; 87.3	59.7	20.0; 21.0; 30.8	55.2; 126.9; 128.2; 128.9. 139.7
4f	122.8; 127.5; 128.0; 131.6	84.9; 88.4	61.8	128.0; 128.4; 137.6	49.7; 66.9
4g	14.0; 18.6; 22.5; 28.4; 29.1; 31.2	77.0; 85.6	59.1	19.8; 20.8; 30.8	54.8; 126.6; 128.0; 128.7; 139.9
4h	13.5; 18.3; 21.8; 31.0	74.6; 84.8	53.7		14.0; 22.6; 27.4; 27.5; 29.2; 29.5; 31.8; 42.1
4i	123.3; 127.3; 128.2; 131.7	86.0; 87.8	62.3	127.9; 128.2; 138.6	24.4; 26.1; 50.6
4j	14.0; 18.6; 22.5; 28.5; 29.1; 31.3	77.6; 85.3	62.2	19.0; 20.1; 31.7	23.4; 50.3
4k	123.1; 127.8; 128.1; 131.6	86.0; 87.0	57.7	13.7; 19.7; 34.9	49.6; 67.0
4l	14.0; 18.6; 22.5; 28.5; 29.0; 31.2	77.1; 86.0	57.3	13.8; 19.8; 35.3	49.5; 67.0
4m	123.1; 127.7; 128.0; 131.5	85.9; 87.0	57.9	13.9; 22.5; 26.4; 29.0; 29.2; 31.6; 32.8	49.6; 66.9
4n	14.0; 18.5; 22.4; 28.4; 28.9; 31.2	77.2; 85.9	57.6	13.9; 22.5; 26.5; 29.1; 29.2; 31.7; 33.1	49.5; 67.0

[a] Literature data (Ref. 11): δ = 24.0; 43.9; 52.7; 84.5; 123.6; 128.0; 128.3; 131.8.

followed by the addition of the appropriate benzotriazole adduct **1** (5 mmol) dissolved in THF (30 mL). After 1 h, the reaction is quenched with a few drops of H_2O, the solvent is evaporated under reduced pressure, and the residue is partitioned between Et_2O (150 mL) and 1 N aqueous NaOH (50 mL). The aqueous layer is extracted with Et_2O (50 mL) and the combined organic solutions are washed with H_2O (100 mL), dried ($MgSO_4$), and evaporated under reduced pressure. The oily residue is purified as indicated in Table 1.

Propargylamines 4i–n; General Procedure:
To the lithium acetylenide **3** (5 mmol), prepared as indicated above, the appropriate benzotriazole adduct **1** (5 mmol) in a benzene solution is added and the reaction proceeds as described above. The oily products are purified by column chromatography on silica gel, using as eluents the solvents indicated in Table 1 for the individual compounds.

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