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N-Triphenylphosphorylidene-1-(benzotriazol-1-yl)methylamine, a Novel Synthon Equivalent to $^{+}CH_2NH_2$: The Preparation of Primary Amines

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Summary: Primary amines are readily prepared by reaction of the title compound with organolithiums or Grignard reagents.

The preparation of primary amines has been accomplished by the connection of a H_2N-CH_2 fragment to a functionalized carbon atom, both by using nucleophilic and by using electrophilic aminomethylation reactions. The substitution of a leaving group (often a halogen atom) by cyanide[1] or by nitromethonium anion,[2] followed by reduction, represents classical, and widely used, examples of the nucleophilic version.

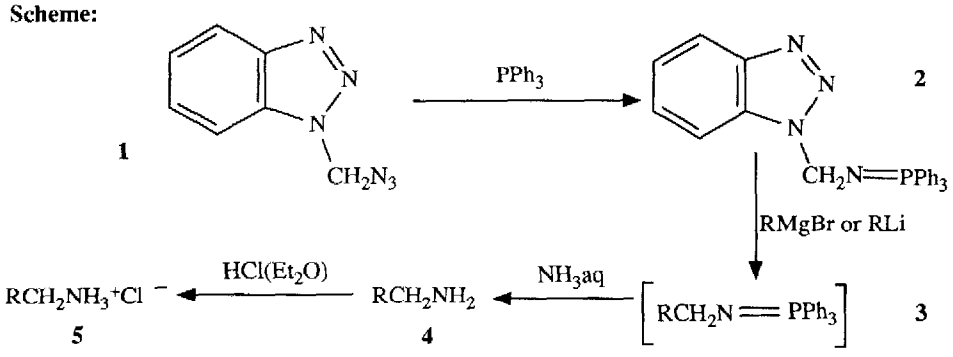
However, the similar conversion of a carbanion (i. e. an organometallic reagent) to a one carbon higher homologous primary amine has attracted much less attention. Additions of organometallic reagents to C=N double- or C≡N triple bonds (nitriles,[3] hydrazones,[4] or alkylidenarenesulfenamides[5]) followed by hydrogenation (for hydrazones and nitriles) or hydrolysis (for alkylidenarenesulfenamides) do result in primary amines, but in those with α-branched carbon skeletons. Similarly, the addition of Grignard reagents to the C=N double bond of ethyl N-diphenylphosphinylformimidate, $Ph_2P(O)N{=}CHOEt$,[6] and simultaneous substitution of the ethoxy group gives -- after deprotection -- secondary alkyl primary amines, R_2CHNH_2, in high yield.

Recently, Japanese[7] and German[8] groups reported, simultaneously but independently, on N,N-bis(trimethylsilyl)methoxymethylamine, a synthon equivalent to $^{+}CH_2NH_2$, and on the application of this reagent for the synthesis of primary amines by reactions with organometallic reagents. However, the method has some drawbacks. The reagent requires tedious preparation from hexamethyldisilazane through lithium- or sodium-bistrimethylsilylamide,[9] by reaction with the expensive and highly carcinogenic chloromethyl methyl ether, and the chemical yield of the protected amines is only moderate in some cases.

We now describe the preparation of N-triphenylphosphorylidene-1-(benzotriazol-1-yl) methylamine (**2**), a novel, and more convenient $^{+}CH_2NH_2$ equivalent synthon, and the application of this new reagent for the one-pot preparation of primary amines of type R-CH_2NH_2.

Preparation of **2** is conveniently accomplished by Staudinger phosphorylation of the easily available 1-azidomethylbenzotriazole (**1**)[10] in an inert organic solvent at room temperature in nearly quantitative yield. The isolated product **2** is a white solid, stable to prolonged storage at room temperature.

Scheme:



The benzotriazole moiety of **2** can be replaced by organometallic (Grignard or lithium) reagents, similar to other 1-benzotriazolylalkylamine derivatives (Mannich adducts).[11] The resulting phosphazenes **3**, without isolation, undergo spontaneous hydrolysis[12] during the basic workup procedure to give primary amines (**4**) which are conveniently converted for isolation into hydrochlorides **5**. The side product benzotriazole is removed with the basic aqueous layer in the extraction step, while the triphenylphosphine oxide remains in the ethereal mother liquor during the isolation of the hydrochloride **5**.

The examples in the Table demonstrate the versatility of the procedure; alkyl, cycloalkyl, aralkyl, aryl, and heteroaryl Grignards and phenylacetylene lithium give equally good yields. The yields are significantly higher than those obtained in comparable cases by the use of N,N-bis(trimethylsilyl)methoxymethylamine: e. g. 77% for cyclohexylamine•HCl, and 86% for phenylpropargylamine•HCl, vs. 52% and 61%,[7] respectively, obtained for the bis-TMS protected products. Moreover, phosphazene **2** need not necessarily be isolated, as demonstrated by the one-pot preparation of benzylamine hydrochloride from azide **1** (Procedure "B").

The unique twofold chemical character of synthon **2** provides wider possibilities. First, the benzotriazole displacing nucleophile can be varied, as described[13] to some extent for the N,N-bis(trimethylsilyl)methoxymethylamine. Furthermore, the phosphazene structure can not only be deprotected by hydrolysis, but also can be subjected *in situ* to various known[14] phosphazene transformations to result in wide variety of compounds of general structure $RCH_2N{=}X$. We plan to continue our work in these directions.

Table. Preparation of Primary Amine Hydrochlorides (5)

$$\underset{\textbf{2}}{R\text{-}X + Bt\text{-}CH_2\text{-}N{=}PPh_3} \longrightarrow \underset{\textbf{5}}{R\text{-}CH_2NH_3{}^+Cl^-}$$

No.	R	X[a]	Method	Yield[b] (%)	Mp. (°C)	Lit. mp. (°C)
5a	$C_6H_5CH_2$	MgCl	A	65	220-221 [c]	216-217[15a]
5b	C_6H_5	MgBr	B	82	255-256 [d]	253[15b]
5c	n-$C_{12}H_{25}$	MgBr	A	87	150 (dec.) [d]	160 (dec.)[15c]
5d	$C_6H_5C{\equiv}C$	Li	A	86	222-223[c]	216-217[16]
5e	c-C_6H_{11}	MgBr	A	77	254-257 [c]	254[15d]
5f	2-thienyl	MgBr	A	84	199-200 [c]	193-194[15e]
5g	1-naphthyl	MgBr	A	93	264-266 [d]	262-264[15f]

[a] All organometallic reagents are prepared freshly in dry Et_2O by standard methods.

[b] Yield of crude products; all crude products gave clear ^1H and ^{13}C n.m.r. spectra.

[c] Melting point obtained after recrystallization from ethanol-acetone mixture.

[d] Melting point of crude product.

Experimental

Preparation of N-Triphenylphosphorylidene-1-(benzotriazol-1-yl)methylamine (**2**)

To a stirred solution of 1-azidomethylbenzotriazole[10] (**1**) (68 mmol 11.8 g) in benzene (100 mL), is added dropwise PPh_3 (68.6 mmol 18.0 g) in benzene (50 mL). After stirring for 2 hrs at room temperature, the solvent is removed on the rotavapor. The residue is washed with anhydrous diethyl ether to give 26 g (95%) white solid. mp.: 99-101 °C; n.m.r. (run on Varian VXR-300 instrument, FT mode, in $CDCl_3$): ^1H(δppm/TMS) : 7.92-7.24, m, 19H (aromatic), 6.11d, (J=30Hz), 2H, (CH_2); ^{13}C(δppm/$CDCl_3$): 146.2, 132.7, 126.2, 123.2, 119.3, 111.6 (Bt); 132.5, 132.4, 131.7, 131.6, 130.4, 129 .1, 128.5, 128.4 (Ph), 62.45 and 62.40 (CH_2); Analysis: for $C_{25}H_{21}N_4P$ calculated: C: 73.52, H: 5.18, N: 13.72; found C: 73.30, H: 5.16, N: 13.60%

Representative procedures for preparation of primary amine hydrochlorides (5)

Method "A"

2-Phenylethylamine Hydrochloride (**5a**)

Benzylmagnesium chloride (15 mmol) in diethyl ether (30 mL) is added to a stirred solution of **2** (12 mmol) in THF (25 mL) over 20 min. and the reaction mixture is stirred overnight at room temperature.

Saturated ammonium chloride (15 mL), then concentrated ammonium hydroxide (20 mL) are added, and after stirring for 1 hr the mixture is extracted with diethyl ether (3 x 60 mL). The combined organic phase is washed with 1 M NaOH (2 x 15 mL), dried with $MgSO_4$ and evaporated. The residue is dissolved in anhydrous diethyl ether (20mL) and saturated ethereal HCl (20mL) solution is added to precipitate the amine hydrochloride. The product is filtered off and washed with anhydrous diethyl ether and acetone to give a white solid (1.23 g, 67%, mp.: 220-221°C).

Method "B", one-pot conversion of **1** to **5**

Benzylamine hydrochloride (**5b**)

To a solution of 1-azidomethylbenzotriazole (**1**) (1.4 g, 8 mmol) in THF (15 mL), is added PPh_3 (2.1 g, 8 mmol) in THF (15 mL). After stirring for 10 min no further nitrogen evolution can be observed. Phenylmagnesium chloride (10 mmol) in ether (25 mL) is added dropwise over 20 min and the same treatment as that in Method "A" then gives benzylamine hydrochloride (0.95 g, 82%, mp.: 255-256°C).

References

1. J. R. Malpass, in: Barton and Ollis Comprehensive Organic Chemistry, Vol. 2, Sutherland, I. O. (ed.), Pergamon Press, Oxford, 1979, p. 9.
2. A. Hamdan, and J. W. F. Wasley, *Synthetic Comm.*, **15**(1), 71 (1985).
3. G. Alvernhe, and A. Laurent, *Tetrahedron Lett.*, 1057 (1973).
4. J. R. Malpass, in: Barton and Ollis Comprehensive Organic Chemistry, Vol. 2, Sutherland, I. O. (ed.), Pergamon Press, Oxford, 1979, p. 15.
5. F. A. Davis, and P. A. Mancinelli, *J. Org. Chem.*, **42**, 398 (1977).
6. A. Zwierzak, and E. Slusarska, *Synthesis*, 691 (1979).
7. T. Morimoto, T. Takahashi, and M. Sekiya, *J. Chem. Soc. Chem. Commun.*, 794 (1984).
8. H. J. Bestmann and G. Wölfel, *Angew. Chem. Int. Ed. Engl.*, **23**(1), 53 (1984).
9. U. Wannagat, and H. Niederprüm, *Chem. Ber.*, **94**, 1540 (1961).
10. A. R. Katritzky, S. Rachwal, K. C. Caster, and F. Mahni, *J. Chem. Soc., Perkin Trans. 1*, 781 (1987).
11. (a) A. R. Katritzky, S. Rachwal, and B. Rachwal, *J. Chem. Soc., Perkin Trans. 1*, 805 (1987).
    (b) A. R. Katritzky, K. Yannakopoulou, Ping Lue, D. Rasala, and L. Urogdi, *J. Chem. Soc., Perkin Trans. 1*, 225 (1989).
    (c) A. R. Katritzky, J. K. Gallos, and K. Yannakopoulou, *Synthesis*, 31 (1989).
    (d) A. R. Katritzky, L. Urogdi, and A. Mayence, *Synthesis*, in press (1989).
12. (a) M. Vaultier, N. Knouzi, and R. Carrié, *Tetrahedron Lett.*, **24**(8), 763 (1983).
    (b) N. Knouzi, M. Vaultier, and R. Carrié, *Bull. Soc. Chim. France*, 815 (1985).
13. (a) T. Morimoto, M. Aono, and M. Sekiya, *J. Chem. Soc., Chem. Commun.*, 1055 (1984).
    (b) K. Okano, T. Morimoto, and M. Sekiya, *J. Chem. Soc., Chem. Commun.*, 883 (1984).
14. J. H. Smith, in: Barton and Ollis Comprehensive Organic Chemistry, Vol. 2, Sutherland, I. O. (ed.), Pergamon Press, Oxford, 1979, p. 1307.
15. Beilsteins Handbuch der Organischen Chemie; Verlag von Julius Springer, Berlin, (a) **12**, 1096; (b) **12**, I, 445; (c) **4**, 201; (d) **12**, 12; (e)**18**, IV, 7097; (f) **12**, II, 740.
16. L. H. Klemm, T. M. McGuire, and K. W. Gopinath, *J. Org. Chem.*, **41**, 2571 (1976).

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