Tetrahedron Letters,Vol.25,No.4,pp 429-432,1984
Printed in Great Britain

0040-4039/84 $3.00 + .00

NEW METHODS AND REAGENTS IN ORGANIC SYNTHESIS. 40.[1] AMINATION OF AROMATIC AND HETEROAROMATIC ORGANOMETALLICS USING DIPHENYL PHOSPHORAZIDATE (DPPA)[2]

Shigehiro Mori, Toyohiko Aoyama, and Takayuki Shioiri*

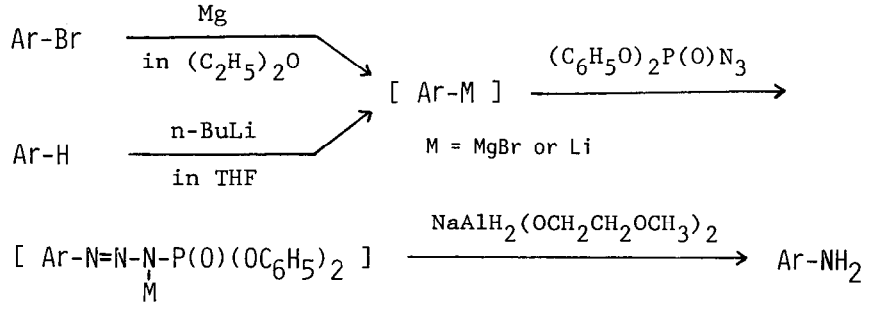
Faculty of Pharmaceutical Sciences, Nagoya City University
Tanabe-dori, Mizuho-ku, Nagoya 467, JAPAN

Amination of aromatic and heteroaromatic organometallics is efficiently achieved by sequential treatment with diphenyl phosphorazidate (DPPA) and sodium bis(2-methoxyethoxy)aluminum hydride in a one-pot process.

Recent publication from our laboratories has disclosed that diphenyl phosphorazidate (DPPA, $(C_6H_5O)_2P(O)N_3$) is very useful as a diazo-transfer reagent[3] in the preparation of trimethylsilyldiazomethane[4] from trimethylsilylmethylmagnesium chloride. Further interest on the use of DPPA as a reagent for the introduction of a nitrogen function led us to investigate the reaction of DPPA with organometallics derived from aromatic and heteroaromatic compounds.

Reaction of organic azides with organometallics (Grignard and lithium compounds) is well known to give 1,3-disubstituted triazenes.[5] Several reports[6-9] on the conversion of triazenes to amines by reductive[6,9] or hydrolytic[7,8] work-up have appeared recently. Although the overall process provides a method for the preparation of aromatic and/or heteroaromatic amines,[10] they have such drawbacks that the triazene formation is limitted to either Grignard[6,7] or lithium[8] compounds, or extension of the amination reaction to heteroaromatic organometallics is not promising.[7] A recent report[9] on the orthoamination of lithiated tertiary benzamides prompts us to disclose our results on the amination of aromatic and heteroaromatic organometallics using DPPA.

We have found that DPPA easily reacts with aromatic and heteroaromatic organometallics (Grignard and lithium compounds) to give phosphoryltriazenes, which are treated with sodium bis(2-methoxyethoxy)aluminum hydride to give amino compounds in good yields.

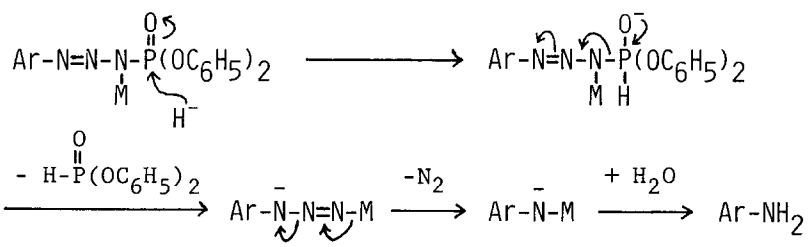


Both Grignard and lithium compounds smoothly react with DPPA under mild conditions. In most cases, diethyl ether is a solvent of choice in the use of Grignard compounds, but tetrahydrofuran is preferable in the case of lithiated compounds. Phosphoryltriazene intermediates can be isolated though they are rather labile. Better results are obtained by the direct reduction of crude triazenes in the same reaction vessel with sodium bis(2-methoxyethoxy)-aluminum hydride. Lithium aluminum hydride also accomplishes the decomposition of triazenes to give amines, but a toluene solution of sodium bis(2-methoxyethoxy)aluminum hydride is much easier to handle in this reaction. Methanolic hydrogen chloride or potassium hydroxide may be used to decompose triazenes, but the efficiency is much lower.

The results are summarized in Table. As compared with the reported procedure for the amination,[6,7a,8,10a-c] the efficiency of our method is either superior or comparable. A number of aromatic bromides were converted to the corresponding amines in good yields. 2-Bromodibenzofuran also underwent the amination smoothly. Ortholithiated aromatic compounds afforded the corresponding amines in modest to good yields. Extension of the method to lithiated heteroaromatic compounds produced amino heteroaromatic compounds smoothly.

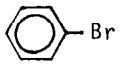
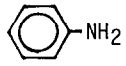
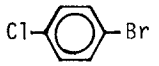
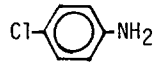
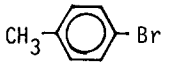
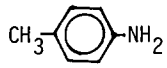
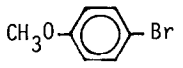
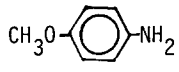
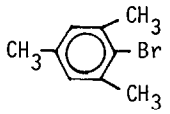
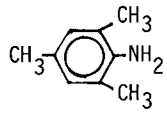
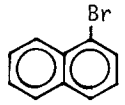
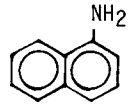
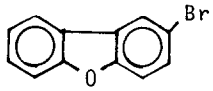
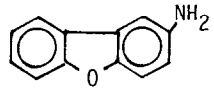
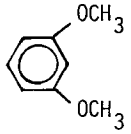
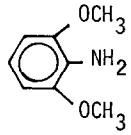
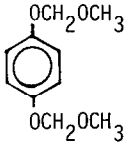
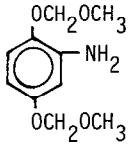
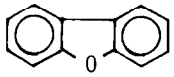
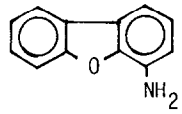
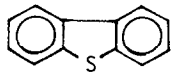
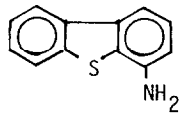
A typical experimental procedure for the amination is as follows: p-Tolylmagnesium bromide in diethyl ether (1.49 ml, 0.74 mM/ml, 1.1 mmol), prepared from 4-bromotoluene and magnesium turnings in diethyl ether, was added dropwise to DPPA (275 mg, 1 mmol) in diethyl ether (10 ml) at -72°C under argon. The mixture was stirred at -72°C for 2 h, then warmed to -20°C during 40 min.[11] After the mixture was again cooled, sodium bis(2-methoxyethoxy)aluminum hydride in toluene (1.23 ml, 70 w/w%, 4.4 mmol) was added at -70°C. The mixture was stirred at 0°C for 1 h, then at room temperature for 0.5 h. Ice-water was carefully added to the mixture, which was filtered and washed with water, benzene, and diethyl ether. The combined filtrate was salted out by the addition of sodium chloride, and the separated organic layer was washed successively with 1% aqueous sodium hydroxide and saturated aqueous sodium chloride, and dried over sodium sulfate.[12] Methanolic hydrogen chloride (5%, ca. 3 ml) was added, and the mixture was concentrated in vacuo to give the solid residue, which was washed with diethyl ether to give p-toluidine hydrochloride (126 mg, 88%).

Reaction mechamism of the reductive decomposition of phosphoryltriazenes with hydride reagents will be presumably as follows:



Amination of aromatic and heteroaromatic organometallics using DPPA appears to be a most promising procedure because of its generality, mildness, rapidity, and high-yield process. Extension of the method to the preparation of medicinally interesting compounds is now actively under way in our laboratories.

Table. Amination of Aromatic and Heteroaromatic Organometallics using DPPA

Run	Starting Material	Product	Reaction Solvent	Yield, %	Reported Yield, %
1			Et_2O	73[a]	67.5,[7a] 68,[8] 90,[10a] 67,[10b] 35[10c]
2			Et_2O	79[a]	49[6]
3			Et_2O	88[a]	66[6]
4			THF	84	51,[6] 50[7a]
5			Et_2O	67	—
6			Et_2O	89	51[10c]
7			THF	71	—
8			THF	72	50-67,[7a] 70[8]
9			THF	47	—
10			THF	58[b] (88)[c]	—
11			THF	62[b] (99)[c]	55[10a]

a Isolated as the hydrochloride.

b Yield based upon starting material.

c Yield based upon consumed starting material.

References and Notes

1 For Part 39, see S. Harusawa, R. Yoneda, T. Kurihara, Y. Hamada, and T. Shioiri, Tetrahedron Lett., submitted.

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4 For a recent preparative use of trimethylsilyldiazomethane, see T. Aoyama, S. Toyama, N. Tamaki, and T. Shioiri, Chem. Pharm. Bull., 31, 2957 (1983).

5 The reaction was discovered by O. Dimroth, Ber., 36, 909 (1903); Ber., 38, 670 (1905); Ber., 39, 3905 (1906).

6 P.A.S. Smith, C.D. Rowe, and L.B. Bruner, J. Org. Chem., 34, 3430 (1969).

7 a) B.M. Trost and W.H. Pearson, J. Am. Chem. Soc., 103, 2483 (1981). b) B.M. Trost and W.H. Pearson, Tetrahedron Lett., 24, 269 (1983). c) B.M. Trost and W.H. Pearson, J. Am. Chem. Soc., 105, 1054 (1983).

8 A. Hassner, P. Munger, and B.A. Belinka, Jr., Tetrahedron Lett., 23, 699 (1982).

9 J.N. Reed and V. Snieckus, Tetrahedron Lett., 24, 3795 (1983).

10 Reports on the direct electrophilic amination of organometallics have also appeared recently; see a) P. Beak and B.J. Kokko, J. Org. Chem., 47, 2822 (1982) and references therein; b) E.W. Colvin, G.W. Kirby, and A.C. Wilson, Tetrahedron Lett., 23, 3835 (1982); c) G. Boche, M. Bernheim, and W. Schrott, Tetrahedron Lett., 23, 5399 (1982); d) G. Boche and W. Schrott, Tetrahedron Lett., 23, 5403 (1982).

11 In the case of the lithiation followed by the amination, n-butyllithium was used in tetrahydrofuran for the ortholithiation and warming up to -20°C was not necessary for the reaction with DPPA.

12 Free amines were obtained at this stage by removal of the solvent, followed by purification of the concentrated residue.

(Received in Japan 7 October 1983)