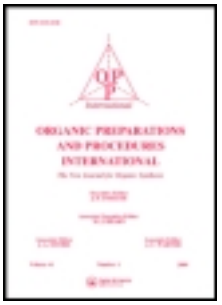

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BENZOTRIAZOLE-MEDIATED SYNTHESIS OF N-ALKYL-N,N'-DIARYLHYDRAZINES

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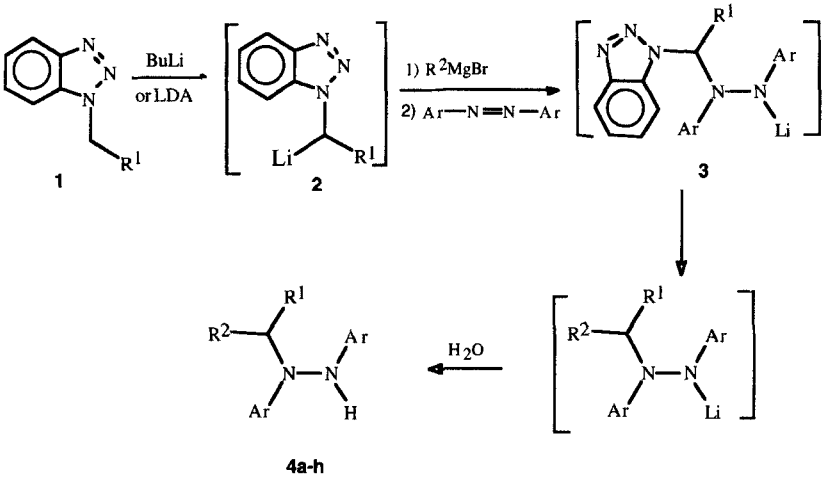
The best method for the preparation of trisubstituted hydrazines is the addition of alkyl- and aryllithiums to the -N=N- bond of azo compounds; however, until recently only strongly π-deficient azodicarboxylate esters have demonstrated real synthetic utility in such reactions.[1,2] The most common alternative access to trisubstituted hydrazines, *via* alkylation of mono- or disubstituted hydrazines, rarely gives good results,[3] but some trisubstituted hydrazines have been prepared by electrophilic amination.[4] We have recently shown that good yields of trisubstituted hydrazines can also be obtained *via* addition of alkyl- or aryllithiums to diarylazobenzenes.[5] A limitation in the construction of specifically trisubstituted hydrazines is the accessibility of the corresponding lithium carbanions. Unfortunately, lithium derivatives cannot be replaced by other carbanion sources, such as Grignard reagents, as these alternatives usually result in one-electron reduction of the azo compounds.[6] Benzotriazole is an important synthetic auxiliary which has the ability to undergo facile replacement by Grignard reagents.[7] We now report that a great variety of substituents can be made available for addition to the -N=N- bond of azobenzenes using α-lithio-1-alkylbenzotriazoles (**2**).

After the addition, substitution of the benzotriazole moiety in **3** with a Grignard reagent affords the desired trisubstituted hydrazines **4** (Scheme 1). By use of this methodology, novel hydrazines **4a-h** were prepared in moderate yields in a one-pot procedure involving deprotonation of the readily available[8] 1-alkylbenzotriazole derivatives **1** with *n*-butyllithium or LDA and subsequent addition of the corresponding Grignard reagent and azobenzenes at -78° under nitrogen.

It is important that intermediates **3** be trapped immediately after generation, as they are highly reactive and decompose rapidly. Consequently, the best yields of hydrazines **4** were achieved when the Grignard reagents were added to the reaction mixture *prior* to the azobenzenes. Grignard reagents react with azobenzenes by oxidation-reduction quite slowly at -78°. However, they undergo transmetallation with lithium derivatives **2**, and the lithium derivatives generated undergo side-addition to the azobenzenes. Thus, we obtained ~ 10% of hydrazines substituted with a group from the Grignard reagent in addition to the target hydrazines **4**. Solid compounds **4c-h** (R^1 = Ar) were purified

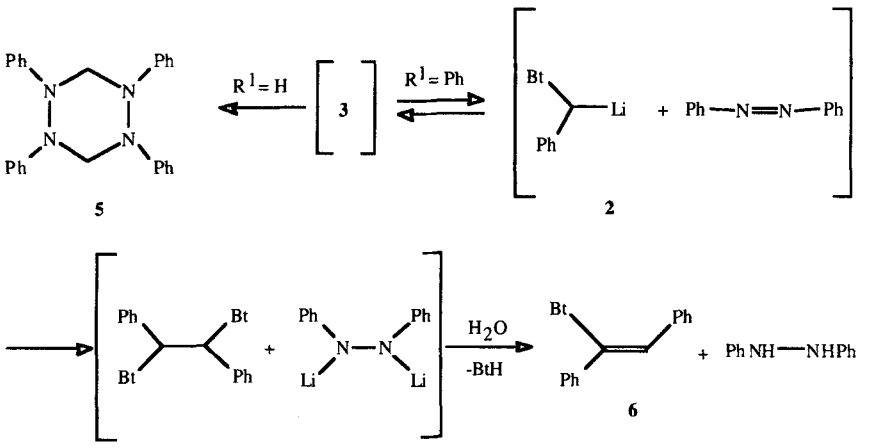
SCHEME 1



by column chromatography. Oily hydrazines **4a,b** were not separated from 1,2-diphenyl-*n*-butylhydrazine and these mixtures were characterized only by NMR spectra.

When the Grignard reagents were added to the reaction mixtures immediately following the azobenzenes, the yields of hydrazines **4** decreased to 15% or less. When no Grignard reagent was added, reaction of the lithium salt of 1-methylbenzotriazole with azobenzene, only hexahydrotetrazine **5** (11%) was isolated from the complex mixture of products. It was apparently generated from two molecules of **3** by elimination of benzotriazole (Scheme 2).

SCHEME 2



Bt = Benzotriazol-1-yl

In contrast, in the absence of a Grignard reagent, the only reaction that occurs is between the lithium derivative of 1-benzylbenzotriazole and azobenzene to give stilbene derivative **6** (88%),

apparently *via* one-electron oxidation of **3** by azobenzene followed by radical dimerization and elimination of one molecule of benzotriazole. Half a mole of azobenzene is consumed in this transformation by reduction to 1,2-diphenylhydrazine (Scheme 2).

EXPERIMENTAL SECTION

Melting points were determined with a Kofler hot stage apparatus without correction. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Varian VXR-300 NMR spectrometer (300 MHz) with TMS ($\delta = 0.00$) as the internal reference for ^1H NMR and the central line of $CDCl_3$ ($\delta = 77.0$) as the reference for ^{13}C NMR. Microanalyses were performed on a Carlo Erba 1106 elemental analyzer. THF was distilled from sodium/benzophenone prior to use. Lithiation reactions were carried out under dry nitrogen. All glassware was dried in an oven. All moisture-sensitive reagents were transferred by means of pre-dried syringes.

Synthesis of Trisubstituted Hydrazines 4a-h. Typical Procedure.- To a solution of substituted 1-alkylbenzotriazole (**1**, 2 mmol) in THF (7 mL), *n*-butyllithium (2 mmol) was added dropwise at -78° and the mixture stirred for 10 min. Then, the Grignard reagent [prepared from magnesium (0.13 g, 4 mmol) and halide (4 mmol) in ether (10 mL)] was added at -78° followed by the azobenzene (2 mmol) in THF (4 mL). The reaction mixture was allowed warm to room temperature overnight. The solution was then washed with ammonium chloride (aq.) (30 mL, 10%), extracted with ethyl acetate (2 10 mL) and dried over magnesium sulfate. The solvent was removed to give the crude products. Compounds **4a**, **4b** did not need to be purified further, and **4c-h** were purified by column chromatography (SiO_2, PhMe/hexane = 1:1) (Tables 1 and 2).

TABLE 1. Preparation of Compounds **4a-h**

Cmpd.	R^1	R^2	Ar	yield (%)	mp (°C)	Elemental Analysis (Found) C	H	N
4a	H	*n*-Bu	Ph	34[a]		–	–	–
4b	CH_2=CH-	*n*-Bu	Ph	32[a]		–	–	–
4c	Ph	Me	Ph	40	94-96	83.30 (83.57)	6.99 (7.08)	9.71 (9.75)
4d	Ph	Ph	Ph	52	131-133	85.68 (85.90)	6.33 (6.38)	7.99 (7.96)
4e	Ph	*n*-Bu	Ph	54	138	83.59 (83.68)	7.93 (8.06)	8.48 (8.48
4f	*p*-MePh	*n*-Bu	Ph	57	97-99	83.68 (83.79)	8.19 (8.34)	8.13 (8.13)
4g	Ph	*n*-Bu	*p*-ClPh	51	72-74	69.17 (68.99)	6.06 (6.04)	7.01 (7.04)
4h	Ph	*n*-Bu	*p*-MePh	48	106-107	83.75 (83.45)	8.43 (8.49)	7.81 (7.91)

a) Yield estimated from NMR.

TABLE 2. Spectral Data of Compounds **4a-h**

Cmpd.	^{1}H NMR (δ: ppm, J: Hz)	^{13}C NMR (δ: ppm)
4a	0.87 (t, 3H, J = 7), 1.27-1.40 (m, 4H), 1.55-1.70 (m, 2H), 3.36 (t, 2H, J = 7), 5.42 (s, 1H), 6.64-6.70 (m, 4H), 6.77-6.80 (m, 2H), 7.01-7.13 (m, 4H)	14.0, 22.5, 25.7, 29.3, 51.9, 112.1, 112.7, 118.3, 119.4, 129.2, 129.3, 147.6, 149.7
4b	0.82 (t, 3H, J = 7), 1.20-1.46 (m, 4H), 1.60-1.70 (m, 2H), 4.24 (m, 1H), 4.30 (m, 1H), 5.10-5.20 (m, 2H), 5.40 (s, 1H), 5.72-5.80 (m, 1H), 6.63-6.72 (m, 4H), 6.74-6.83 (m, 2H), 7.01-7.12 (m, 4H)	14.0, 22.6, 28.9, 63.7, 112.0, 112.1, 112.2, 114.3, 117.6, 118.3, 128.6, 129.1, 148.8, 152.6
4c	1.63 (d, 3H, J = 7), 5.27 (br s, 2H), 6.75-6.79 (m, 4H), 6.90-6.93 (m, 2H), 7.12-7.29 (m, 9H)	18.1, 59.8, 111.9, 112.0, 114.4, 119.1, 119.2, 127.3, 128.4, 129.0, 129.2, 148.8, 149.6
4d	5.47 (s, 1H), 6.22 (s, 1H), 6.59-6.63 (m, 2H), 6.66-6.72 (m, 1H), 6.81-6.86 (m, 1H), 6.92-6.95 (m, 2H), 7.01-7.07 (m, 2H), 7.16-7.26 (m, 12H)	70.8, 112.6, 115.3, 119.2, 119.4, 123.3, 127.3, 128.2, 128.9, 129.0, 129.1, 139.5, 147.6, 150.3
4e	0.87 (t, 3H, J = 7), 1.29-1.56 (m, 4H), 1.91-2.05 (m, 1H), 2.08-2.20 (m, 1H), 4.98 (t, 1H, J = 7), 5.07 (br s, 1H), 6.71-6.82 (m, 4H), 6.92-6.96 (m, 2H), 7.10-7.25 (m, 9H)	14.1, 22.7, 29.4, 31.1, 67.2, 112.3, 115.2, 119.1, 119.6, 127.6, 128.3, 129.2, 148.5, 150.2
4f	0.88 (t, 3H, J = 7), 1.26-1.57 (m, 4H), 1.86-2.01 (m, 1H), 2.06-2.18 (m, 1H), 2.28 (s, 3H), 4.94 (t, 1H, J = 7), 5.07 (br s, 1H), 6.68-6.81 (m, 4H), 6.93 (d, 2H, J = 8), 7.04-7.20 (m, 8H)	14.1, 21.1, 22.7, 29.4, 31.2, 66.0, 112.2, 115.2, 119.0, 119.5, 128.1, 128.9, 129.1, 137.1, 148.5, 150.3
4g	0.87 (t, 3H, J = 7), 1.25-1.53 (m, 4H), 1.92-1.97 (m, 1H), 2.01-2.10 (m, 1H), 4.89 (t, 1H, J = 7), 5.07 (br s, 1H), 6.66, 7.08 (AB, 4H, J = 8), 6.85, 7.18 (AB, 4H, J = 8), 7.18-7.22 (m, 2H), 7.23-7.31 (m, 3H)	14.0, 22.7, 29.4, 30.9, 66.8, 113.4, 116.5, 123.8, 124.8, 127.9, 128.1, 128.4, 129.1, 139.0, 146.6, 148.6
4h	0.87 (t, 3H, J = 7), 1.33-1.55 (m, 4H), 1.87-2.02 (m, 1H), 2.08-2.33 (m, 1H), 2.21 (s, 3H), 2.22 (s, 3H), 4.89 (t, 1H, J = 7), 4.96 (br s, 1H), 6.67, 6.92 (AB, 4H, J = 8.2), 6.82, 6.98 (AB, 4H, J = 8.7), 7.22-7.24 (m, 5H)	14.1, 20.4, 20.5, 22.7, 29.5, 31.2, 66.4, 112.3, 115.4, 127.4, 128.1, 128.3, 128.8, 129.6, 146.3, 147.9

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