

A Convenient, One-Pot Preparative Method for Tri- and Tetrasubstituted Hydrazines from Azobenzenes and Organolithiums

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Organolithiums add smoothly to the N=N bond of azobenzenes at -78°C to give the lithium derivative of the trisubstituted hydrazine. The corresponding trisubstituted hydrazines, or a variety of unsymmetrically tetrasubstituted hydrazines, were thus conveniently prepared in high yielding one-pot procedures by direct quench, or by treatment of the reaction mixture with an alkyl iodide prior to workup.

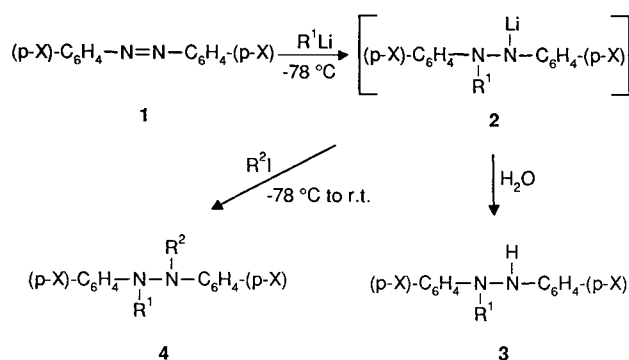
Hydrazines form an important class of organic compounds which has many applications in organic synthesis as well as in industry. Photoconductive coated film containing tetraarylhydrazines is used in electrophotographic photoconductors to give excellent electrophotographic performance.¹ Hydrazines, particularly when tetrasubstituted, are an excellent source of radical cations.^{2–8} Tetraalkylhydrazines are also frequently employed in the study of single-electron transfer reactions,^{5–8} and as charge-transfer quenchers of singlet oxygen.⁴

Tetraalkyl-, symmetrical 1,2-diaryl-1,2-dialkyl- and symmetrical tetraarylhydrazines have been prepared in a number of different ways, including oxidative *N,N*-coupling of disubstituted amines to give the corresponding symmetrical tetrasubstituted hydrazines,^{9–11} reduction of both carbonyl groups of 1,2-diacyl-1,2-disubstituted hydrazines with lithium aluminium hydride^{12–15} or borane,¹⁶ direct alkylation of trisubstituted hydrazines with alkyl halides¹⁷ or reductive alkylation with aldehydes.⁸ Surprisingly, unsymmetrical 1,2-diaryl-1,2-dialkyl- and 1,1,2-triaryl-2-alkylhydrazines were previously completely unknown classes.¹⁸ We now report a convenient, one-pot preparative method from azobenzenes and organolithiums: the first general method for unsymmetrical tetrasubstituted hydrazines and the best route to many trisubstituted hydrazines.

A few examples are available in the literature for reactions of organolithiums with azocompounds. However, the synthetic utility of this reaction has not been developed. Phenyllithium reacts with azobenzene to give triphenylhydrazine (20% yield),¹⁹ with benzo[*c*]cinnoline to give 5,6-dihydro-5-phenylbenzo[*c*]cinnoline (unspecified yield),²⁰ and with 2,3-diazobicyclo[2.2.2]oct-2-ene, followed by subsequent reaction with 4-nitrofluorobenzene, to give 2-(4-nitrophenyl)-3-phenyl-2,3-diazobicyclo[2.2.2]octane (34%).²¹ The analogous reaction of *tert*-butyllithium with 2,3-diazobicyclo[2.2.1]hept-2-ene gives 2-*tert*-butyl-2,3-diazobicyclo[2.2.1]heptane (90%).²² Grignard reagents add to the N=N bond of azodicarboxylic ester.²³ The first systematic investigation of this route as a synthetic method for trisubstituted hydrazines by Kaiser and Bartling²⁴ found that the lithium salts of active hydrogen compounds (e.g., diphenylmethane, 4-picoline, 2,4-lutidine) add to the N=N double bond of azobenzene at -78°C to give the corresponding substituted hydrazobenzenes: the use of two equivalents of

carbanions increased the yields (19–63% to 60–97%) and a reversible reaction mechanism was suggested.

We now report that the reaction of azobenzenes with one equivalent of phenyllithium, or *n*-, *sec*-, or *tert*-butyllithium at -78°C in tetrahydrofuran under nitrogen followed by an aqueous quenching gives the expected trisubstituted hydrazines **3** (Scheme, Table 1). Phenyllithium, *n*- and *sec*-butyllithium gave the 1-substituted 1,2-diphenylhydrazines **3a**, **3b**, **3d** in high yields. *tert*-Butyllithium gave **3c** in 47% yield, in contrast to the low yield previously reported (10%).²⁵ The value of the current procedure is demonstrated by the preparation of a new, sterically hindered trisubstituted hydrazine **3b** in 73% yield, while the previously attempted preparation by alkylation of hydrazobenzene with 2-bromobutane failed.²⁶ 1,1,2-Triphenylhydrazine (**3d**) was obtained in 90% yield. Previous preparations^{19,27–31} of this compound all yielded less than 21%, except for a recent report by Barton,³² who used a trivalent organobismuth reagent to achieve a yield of 60%. Compared to the literature, the current procedure is the method of choice for the preparation of 1-alkyl-1,2-diaryl- and triarylhydrazines as it gives the desired products in high yield (even for sterically hindered cases) from readily available starting materials.



Scheme

Interestingly, in contrast to the other trisubstituted hydrazines **3**, both the ^1H and ^{13}C NMR spectra of **3b** (Tables 2–3) showed two sets of signals indicating the existence of two conformers resulting from the slow flipping of the lone electron pair of the N-atom to which the alkyl group is attached. Although slow flipping is typical of hydrazines³⁴ and probably also occurs in **3a** and **3c**, it is detectable only in **3b**, because **3b** contains a chiral C-atom. The two sets of signals for **3b** were poorly separated in the spectra obtained from a CDCl_3 solution; better separation in $\text{DMSO}-d_6$ was observed.

Table 1. Tri- and Tetrasubstituted Hydrazines **3**, **4** Prepared

Product	X	R ¹	R ²	Yield (%)	mp (°C)	
					found	reported
3a ^{a,b}	H	Bu	–	88	oil	–
3b ^b	H	<i>s</i> -Bu	–	73	oil	–
3c ^b	H	<i>t</i> -Bu	–	47	54–56	54–55 ²⁵
3d	H	Ph	–	90	142–143	139 ²⁷
4a	H	Bu	Bu	99	53–55	57.2–57.7 ³³
4b ^b	H	Bu	Et	70	oil	–
4c ^b	H	<i>s</i> -Bu	Me	75	oil	–
4d ^b	H	Ph	Et	72	110–112	–
4e ^b	H	Ph	Bu	64	83–84	–
4f ^b	Me	Bu	Me	73	oil	–
4g ^b	Cl	Bu	Me	82	oil	–

^a ¹H NMR data in agreement with those reported.²⁶

^b Satisfactory elemental analyses were obtained: C ± 0.32, H ± 0.19, N ± 0.50.

Intensities of the aliphatic peaks in the ¹³C NMR spectra (non-quantitative run) obtained from solutions in either CDCl₃ or DMSO-*d*₆ were much smaller than those of the aromatic peaks, and caution should be used when trying to identify this product by ¹³C NMR from crude reaction mixtures.

The current preparative method was successfully extended to a convenient, one-pot procedure for the synthesis of both symmetrically and unsymmetrically tetrasubstituted

hydrazines by the addition of primary alkyl iodides to the reaction mixtures before workup. This gave a variety of tetrasubstituted hydrazines **4** in high yields (Scheme, Table 1). All of the unsymmetrical tetrasubstituted hydrazines prepared **4b–4g** are novel and were characterized by elemental analyses and ¹H and ¹³C NMR spectroscopy (Tables 1–3). The current methodology complements the preparation of aliphatic unsymmetrical tetrasubstituted hydrazines by the addition of alkyllithiums to diazenium salts developed by Nelsen.³⁵

Melting points were determined on a hot-stage microscope and are uncorrected. ¹H and ¹³C NMR spectra were recorded on a Varian VXR 300 spectrometer (300 and 75 MHz, respectively), using CDCl₃ as solvent and TMS as an internal reference. HRMS were recorded on a Kratos AEI MS 30 spectrometer. Elemental analyses were performed on a Carlo Erba 1106 elemental analyzer.

Trisubstituted Hydrazines **3**; General Procedure:

A solution of alkyllithium (11 mmol) in hexane or cyclohexane was added dropwise to a stirred solution of azobenzene (1.82 g, 10 mmol) in 30 mL THF at –78 °C under N₂. The mixture was stirred at this temperature for 2 h, allowed to warm up to r.t. and stirred for another 10 h. The mixture was poured into H₂O (100 mL), extracted with EtOAc (200 mL), washed with H₂O (100 mL), dried (MgSO₄) and concentrated to give hydrazines **3a–3d** which were purified by column chromatography (toluene/hexane, 1:3).

Tetrasubstituted Hydrazines **4**; General Procedure:

A solution of alkyllithium (11 mmol) in hexane or cyclohexane was added dropwise to a solution of azobenzene (1.82 g, 10 mmol) in THF (30 mL) at –78 °C under N₂. After stirring at this temperature

Table 2. ¹H NMR Data of Hydrazines **3** and **4**,^a δ, *J* (Hz)

Product	R ¹	R ² (or NH)	<i>p</i> -X-C ₆ H ₄
3a	0.94 (t, <i>J</i> = 7.4, 3H), 1.37 (sext, <i>J</i> = 7.6, 2H), 1.65 (quint, <i>J</i> = 7.5, 2H), 3.49 (t, <i>J</i> = 7.6, 2H)	5.58 (s, 1H)	6.80 (m, 4H), 6.88 (m, 2H), 7.21 (m, 4H)
3b ^b	0.92 (t, <i>J</i> = 7.4, 3H), 1.13 (d, <i>J</i> = 6.4, 3H), 1.46 (m, 1H), 1.72 (m, 1H), 3.90 (sext, <i>J</i> = 6.9, 1H)	7.00 (s, 1H)	6.60 (t, <i>J</i> = 7.2, 1H), 6.68 (t, <i>J</i> = 7.2, 1H), 6.81 (d, <i>J</i> = 7.8, 2H), 6.88 (d, <i>J</i> = 8.1, 2H), 7.06 (t, <i>J</i> = 7.9, 2H), 7.12 (t, <i>J</i> = 8.0, 2H)
3c	1.18 (s, 9H)	5.62 (s, 1H)	6.65 (m, 1H), 6.90 (m, 2H), 7.05 (m, 1H), 7.10 (m, 2H), 7.20 (m, 4H)
3d	7.17 (m, 1H, overlapping), 7.23 (m, 4H, overlapping)	6.09 (s, 1H)	6.82 (m, 3H), 6.96 (m, 2H), 7.17 (m, 1H, overlapping), 7.23 (m, 4H, overlapping)
4a	0.93 (t, <i>J</i> = 7.3, 3H), 1.35 (sext, <i>J</i> = 7.3, 2H), 1.70 (br, 2H), 3.43 (t, <i>J</i> = 8.1, 2H)	0.93 (t, <i>J</i> = 7.3, 3H), 1.35 (sext, <i>J</i> = 7.3, 2H), 1.70 (br, 2H), 3.43 (t, <i>J</i> = 8.1, 2H)	6.72 (m, 6H), 7.20 (t, <i>J</i> = 8.1, 4H)
4b	0.92 (t, <i>J</i> = 7.3, 3H), 1.34 (sext, <i>J</i> = 7.5, 2H), 1.70 (m, 2H), 3.42 (t, <i>J</i> = 8.0, 2H)	1.26 (t, <i>J</i> = 7.1, 3H), 3.53 (q, <i>J</i> = 7.2, 2H)	6.74 (m, 6H), 7.19 (m, 4H)
4c ^b	0.92 (t, <i>J</i> = 7.5, 3H), 1.17 (d, <i>J</i> = 6.3, 3H), 1.46 (m, 1H), 1.80 (m, 1H), 3.90 (m, 1H)	3.09 (s, 3H)	6.56 (m, 2H), 6.70 (m, 4H), 7.13 (m, 4H)
4d	6.93 (m, 1H), 7.20 (m, 4H)	1.19 (t, <i>J</i> = 7.2, 3H), 3.67 (q, <i>J</i> = 7.2, 2H)	6.74 (m, 1H), 6.83 (d, <i>J</i> = 7.9, 2H), 6.93 (m, 1H), 7.20 (m, 6H)
4e	6.92 (m, 1H), 7.18 (m, 4H)	0.85 (t, <i>J</i> = 7.5, 3H), 1.25 (sext, <i>J</i> = 7.5, 2H), 1.62 (quint, <i>J</i> = 7.5, 2H), 3.57 (t, <i>J</i> = 7.5, 2H)	6.74 (m, 1H), 6.82 (d, <i>J</i> = 8.8, 2H), 6.92 (m, 1H), 7.18 (m, 6H)
4f	0.91 (t, <i>J</i> = 7.5, 3H), 1.34 (sext, <i>J</i> = 7.5, 2H), 1.63 (quint, <i>J</i> = 7.5, 2H), 3.33 (t, <i>J</i> = 7.5, 2H)	3.01 (s, 3H)	2.25 (s, 6H), 6.67 (m, 4H), 7.03 (m, 4H)
4g	0.83 (t, <i>J</i> = 7.5, 3H), 1.26 (sext, <i>J</i> = 7.5, 2H), 1.51 (quint, <i>J</i> = 7.5, 2H), 3.23 (br, 2H)	2.93 (s, 3H)	6.55 (m, 4H), 7.06 (m, 4H)

^a Recorded in CDCl₃ on a Varian VXR-300 spectrometer except as noted otherwise.

^b Measured in DMSO-*d*₆ at 100 °C.

Table 3. ^{13}C NMR Data of Hydrazines **3** and **4**,^a δ

Product	R ¹	R ²	<i>p</i> -X-C ₆ H ₄
3a	14.0, 20.4, 28.1, 51.8	—	112.2, 112.8, 118.4, 119.5, 129.2, 129.3, 147.7, 149.7
3b^b	10.8, 15.3, 25.7, 57.6	—	111.3, 114.0, 117.1, 117.7, 128.1, 128.2, 149.3, 149.6
3c	26.9, 58.7	—	112.7, 118.4, 124.9, 126.3, 128.1, 128.8, 148.3, 149.3
3d	119.0, 122.4, 129.1, 146.6	—	112.1, 119.0, 119.9, 122.4, 129.1, 129.3, 146.6, 147.5
4a	13.9, 20.5, 30.1, 50.9	13.9, 20.5, 30.1, 50.9	112.3, 117.7, 129.2, 148.3
4b	14.1, 20.7, 30.3, 51.0	13.5, 45.1	112.3, 112.6, 117.9, 118.0, 129.4 (2C), 148.2, 148.8
4c^b	10.5, 15.9, 26.4, 56.2	38.8	110.7, 112.7, 116.4, 117.1, 128.2, 128.4, 145.9, 149.8
4d	118.4, 121.8, 129.1, 144.8	16.5, 46.0	111.9, 118.1, 118.4, 121.8, 129.0, 129.3, 144.8, 147.9
4e	118.5, 121.9, 129.1, 144.6	13.8, 20.4, 29.8, 51.2	111.9, 118.1, 118.5, 121.9, 129.1, 129.3, 144.6, 148.0
4f	14.0, 20.6, 30.0, 49.4	35.1	20.3, 111.7, 112.9, 126.6, 127.4, 129.7, 129.8, 145.9, 147.1
4g	13.9, 20.5, 29.7, 49.5	35.3	112.8, 114.0, 122.8, 123.5, 129.1, 129.2, 146.4, 147.5

^a Recorded in CDCl₃ on a Varian VXR-300 spectrometer except as noted otherwise.

^b Measured in DMSO-*d*₆ at 100 °C.

for 30 min, an alkyl iodide (15 mmol for MeI and EtI, 20 mmol for BuI) was added. The reaction mixture was allowed to warm to r. t. and stirred for an additional 24 h, poured into H₂O (100 mL), extracted with EtOAc (200 mL), washed with H₂O (100 mL), dried (MgSO₄) and concentrated to give hydrazines **4a–4g** which were purified by flash column chromatography (hexane). Hydrazines **4** decompose slowly on silica gel.

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