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Facile Synthesis of Mono-, Di-, and Trisubstituted Alpha-Unbranched Hydrazines

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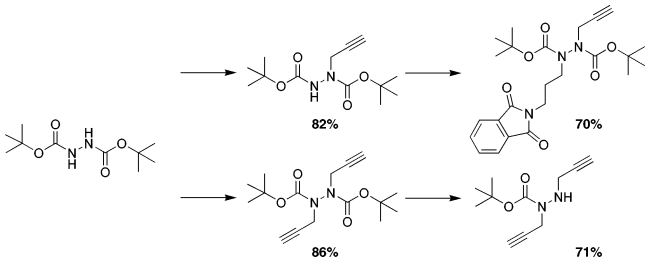


Methods for the alkylation of di-*tert*-butyl hydrazine-1,2-dicarboxylate were investigated. It was found that under mild conditions mono- or di-substituted hydrazine derivatives were obtained in good to excellent yield. Furthermore, it was shown that one of the two Boc-groups of the disubstituted derivatives was selectively removed by heating, leading to precursors for trisubstituted hydrazines.

Substituted alkyl hydrazines are an important class of organic compounds that have found applications in medicinal chemistry and as intermediates in the synthesis of heterocyclic compounds.[1−4] Despite their appealing structural simplicity they are generally difficult to access. Direct synthesis from unprotected hydrazine is known to be difficult and low yielding, generally giving rise to complex mixtures of products.[5] Intensive efforts have led to a variety of useful methods for their synthesis, using orthogonally protected hydrazines. Most of the available methods are limited to yield hydrazines with one specific degree of substitution with only very few of them being truly general.[6−13]

Tri-*tert*-butyl hydrazine-1,1,2-tricarboxylate **1** and *tert*-butyl 2-(propan-2-ylidene)hydrazine carboxylate **2** (Figure 1) have been successfully used in the preparation of monoalkylated hydrazines.[14−16] Both compounds can be alkylated under phase transfer conditions at room temperature and 80 °C, respectively. Deprotection under acidic conditions yields the monosubstituted hydrazines in good to excellent yields.

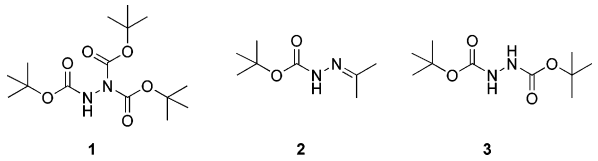
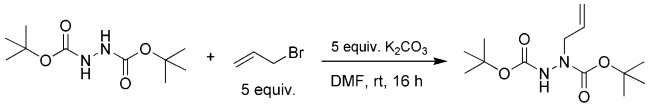


FIGURE 1. Precursors for substituted hydrazines.

Furthermore, in the case of reagent **1** it was found that one of the geminal Boc-groups was selectively removed under mild conditions using magnesium perchlorate in acetonitrile; further alkylation and complete deprotection gave the 1,2-dialkylated hydrazines.[14,15] Compound **1** is now commercially available, and the method is a very useful way for preparing mono- and disubstituted hydrazines. Reagent **2**, though currently not commercially available, is readily synthesized from *tert*-butyl hydrazinecarboxylate and acetone and has been used for the synthesis of monosubstituted hydrazines in good to excellent yields. Unfortunately, it is not suitable for the preparation of more highly substituted derivatives.[16] Several literature reports describe the use of the readily available di-*tert*-butyl hydrazine-1,2-dicarboxylate **3** as a precursor for the preparation of substituted alkyl hydrazines. However, these methods all use harsh reaction conditions, such as strong bases (i.e., *n*-butyllithium or sodium hydride) or high temperatures (80−100 °C).[2−4,17]

In our efforts toward the versatile preparation of substituted alkyl hydrazines we decided to investigate the possibility of selective alkylation of **3**. We found that **3** was selectively monosubstituted using excess allyl bromide and potassium carbonate in dimethylformamide yielding 62% of di-*tert*-butyl 1-allylhydrazine-1,2-dicarboxylate (**4c**) after 16 h at room temperature (Scheme 1).

SCHEME 1. Monoallylation of 3



Interestingly, only very little disubstituted product was observed despite the use of excess allyl bromide. However,

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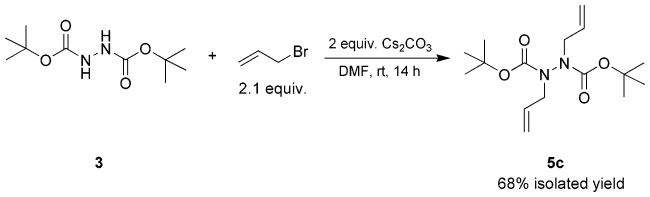
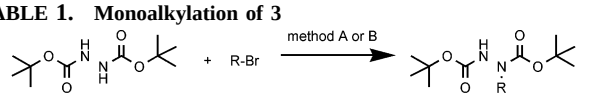
changing the base from potassium carbonate to cesium carbonate led to dialkylation under otherwise identical conditions (Scheme 2).

SCHEME 2. Diallylation of 3



The mild reaction conditions and the fact that mono- or disubstiution can be achieved by simply changing the carbonate base prompted us to look at other alkylating agents. Unfortunately, other alkyl bromides reacted very slowly. For example in the case of propargyl bromide, satisfactory conversion required a reaction time of 1 week at room temperature. Instead it was found that alkylation using propargyl bromide was particular efficient under phase transfer conditions. Hence, the conversion **3** to the monopropargyl derivative was achieved in good yield at room temperature using excess propargyl bromide with tetrabutylammonium hydrogensulfate as phase transfer catalyst in a biphasic mixture of toluene and 5% aqueous sodium hydroxide. These conditions were found to be suitable in the case of propargyl and allyl bromide yielding 82% and 71%, respectively, of the monoalkylated hydrazine derivatives (**4c** and **4d**, Table 1). In the case of less reactive alkylation reagents (**4a** and **4b**, Table 1) excellent yields were obtained using 1.1 equiv of the alkyl bromide and 1 equiv cesium carbonate in dimethylformamide at room temperature. We were thus able to selectively synthesize a diverse range of di-Boc-monosubstituted hydrazines directly from **3**.

TABLE 1. Monoalkylation of 3



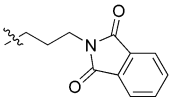
Compound	R	reaction time, h	Yield, %[a]	mp., °C	method[b]
4a		4	86%	103-5	A
4b		4	97%	75-7	A
4c		4 2.5	88% 71%	74	A B
4d		19	82%	103	B

[a] Isolated yield after chromatography. [b] (Method A) 1.1 equiv of alkyl bromide, 1 equiv of Cs_2CO_3, DMF, rt, 4 h; (Method B) 3 equiv of alkyl bromide, $PhCH_3$/5% aq NaOH, TBAHS, rt, 2.5 h for **4c**; 19 h for **4d**.

The symmetrically disubstituted derivatives were easily obtained in good to excellent yields using excess alkyl bromide and 2 equiv of cesium carbonate as shown in Table 2.

Similarly, the unsymmetrically 1,2-disubstituted hydrazine derivatives could be obtained by treatment of the monosubstituted products with cesium carbonate and allyl bromide, benzyl bromide, or 2-(3-bromopropyl)isoindoline-1,3-dione. Examples

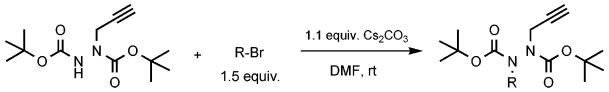
TABLE 2. Dialkylation of 3

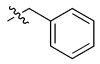
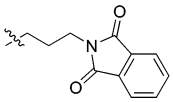
Compound	R	reaction time, h	Yield, %[a]	mp., °C
5a		8	91[b]	104-5
5b		48	70[c]	-
5c		24	68[c]	-
5d		17	86[c]	97-9
5e		19	84[c]	-

[a] Isolated yield after chromatography. [b] 2.2 equiv of benzyl bromide. [c] 4 equiv of alkyl bromide.

are shown in Table 3. Both the symmetrical and unsymmetrical disubstituted derivatives were found to have complicated ^1H and ^{13}C NMR spectra. This has previously been reported and explained by the existence of up to four different conformations in this class of compounds.[14,15]

TABLE 3. Further Alkylation of 4d



Compound	R	reaction time, h	Yield, %[a]
6a		16	67
6b		16	75
6c		16	70

[a] Isolated yield after chromatography.

Analysis of the symmetrical 1,2-disubstituted derivatives (Table 2) by gas chromatography showed the product peak as well as a minor peak (ca. 10%). The appearance of an additional peak, despite the fact that the compounds were all judged pure by TLC as well as LCMS analysis, made us speculate that the compounds could be decomposing in the injector of the GC (T = 225 °C). To confirm this hypothesis compound **5d** was subjected to heating under various conditions. It was found that heating to 185 °C in diphenyl ether for 1.5 h caused the loss of only one of the two Boc-groups yielding 71% of **7** (Scheme 3).

The fortuitous discovery that we can selectively remove one Boc-group enables further reaction to form trisubstituted hydrazines. Thus, treatment of compound **7** with iodomethane gave compound **8** in 50% unoptimized yield after 3 days (Scheme 4).

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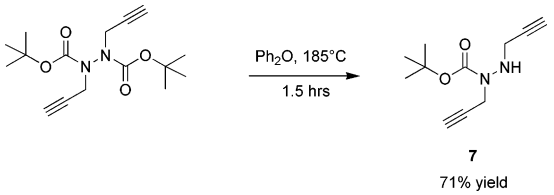
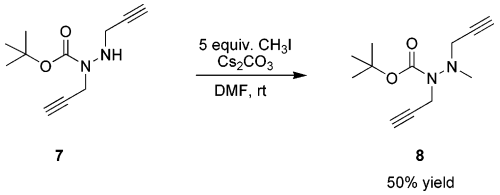
SCHEME 3. Thermal Removal of Boc-group



SCHEME 4. Alkylation of 7



Removal of the Boc-group from all the aforementioned products under standard conditions gives rise to the mono-, di-, and trisubstituted hydrazines.

In summary we have investigated the use of di-*tert*-butyl hydrazine-1,2-dicarboxylate **3** as a precursor for the synthesis of certain mono-, di-, and trisubstituted hydrazines. The ease with which the degree of substitution can be controlled makes this commercially available protected hydrazine a practical and useful precursor for the synthesis of substituted hydrazines and adds to the already existing synthetic methods for achieving substituted hydrazines. Furthermore, we have shown that compounds such as **5a**−**e** upon heating loose one of the two Boc-groups and that the resulting monoprotected hydrazine can be alkylated to yield trisubstituted hydrazines.

Experimental Section

General Procedure for Monoalkylation, Method A, Synthesis of Di-*tert*-butyl 1-Benzylhydrazine-1,2-dicarboxylate 4a: To a solution of di-*tert*-butyl hydrazine-1,2-dicarboxylate (500 mg, 2.15 mmol) in DMF (10 mL) was added cesium carbonate (1.40 g, 4.30 mmol) and benzyl bromide (405 mg, 2.37 mmol). The mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic phases were washed with brine (3 × 20 mL), dried over magnesium sulfate, and concentrated in vacuo. Flash chromatography (ethyl acetate/hexane 1/10) yielded 86% of **4a** as a white solid. ^{1}H NMR (600 MHz, $CDCl_3$, 50 °C) δ 1.43 (s, 9H), 1.48 (s, 9H), 4.62 (bs, 2H), 6.2 (bs, 1H), 7.25−7.32 (m, 5H). ^{13}C NMR (500 MHz, $CDCl_3$, rt) δ 28.4, 53.0, 54.6, 81.4, 127.6, 128.6, 137.4, 155.2. MS (ESI-TOF): calcd for $C_{17}H_{26}N_2O_4Na^+$ (MNa^+), 345.1785; found, 345.1791. Mp 103.1−105.2 °C.

General Procedure for Monoalkylation, Method B, Synthesis of Di-*tert*-butyl 1-Allylhydrazine-1,2-dicarboxylate 4c: Di-*tert*-butyl hydrazine-1,2-dicarboxylate (300 mg, 1.29 mmol) was dissolved in a mixture of toluene (2 mL) and 5% aqueous sodium hydroxide (2 mL). To the biphasic mixture were added tetrabutylammonium hydrogensulfate (10 mg, 0.03 mmol) and allyl bromide (468 mg, 3.87 mmol). The reaction was stirred at room temperature for 2.5 h. Water (20 mL) was added, and the mixture was extracted with ethyl acetate (3 × 15 mL). The combined organic phases were washed with brine (15 mL), dried over magnesium sulfate, and concentrated in vacuo. Flash chromatography (ethyl acetate/hexane 1/14) yielded 88% of **4c** as a white solid. ^{1}H NMR (600 MHz, $CDCl_3$, 50 °C) δ 1.43 (s, 9H), 1.48 (s, 9H), 4.62 (bs, 2H), 6.22 (bs, 1H), 7.25−7.32 (m, 5H). ^{13}C NMR (600 MHz, $CDCl_3$, 50 °C) δ 28.4, 52.7, 53.3, 81.3, 81.4, 117.7, 133.4, 155.3. MS (ESI-TOF): calcd for $C_{13}H_{24}N_2O_4Na^+$ (MNa^+), 295.1628; found, 295.1633. Mp 74.0−74.4 °C.

General Procedure for Dialkylation, Synthesis of Di-*tert*-butyl 1,2-Dibenzylhydrazine-1,2-dicarboxylate 5a: To a solution of di-*tert*-butyl hydrazine-1,2-dicarboxylate (500 mg, 2.15 mmol) in DMF (10 mL) was added cesium carbonate (2.10 g, 6.45 mmol) and benzyl bromide (809 mg, 4.73 mmol). The mixture was stirred at room temperature for 7 h. The crude product was diluted with water (20 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic phases were washed with brine (3 × 20 mL), dried over magnesium sulfate, and concentrated in vacuo. Flash chromatography (ethyl acetate/hexane 1/20) yielded 91% of **5a** as a white solid. ^{1}H NMR (600 MHz, $CDCl_3$, 50 °C) δ 1.32−1.45 (m, 18H), 4.18−4.93 (m, 4H), 7.08−7.27 (m, 10H). ^{13}C NMR (600 MHz, $CDCl_3$, 50 °C) δ 28.8, 53.6, 81.7, 128.3, 129.1, 130.5, 137.8, 155.8. MS (ESI-TOF): calcd for $C_{24}H_{32}N_2O_4Na^+$ (MNa^+), 435.2254; found, 435.2260. Mp 104.5−105.4 °C.

General Procedure Unsymmetrically Disubstituted Derivatives, Synthesis of Di-*tert*-butyl 1-Allyl-2-(prop-2-ynyl)hydrazine-1,2-dicarboxylate 6b: To a solution of **4d** (300 mg, 1.11 mmol) in DMF (6 mL) were added cesium carbonate (398 mg, 1.22 mmol) and allyl bromide (201 mg, 1.66 mmol). The reaction mixture was stirred for 16 h at room temperature. The reaction was diluted with water (20 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic phases were washed with brine (3 × 20 mL), dried over magnesium sulfate, and concentrated in vacuo. Flash chromatography (ethyl acetate/hexane 1/20) yielded 75% of **6b** as a colorless liquid. ^{1}H NMR (600 MHz, $CDCl_3$, 50 °C) δ 1.46 (s, 18H), 2.22 (s, 1H), 4.00−4.59 (m, 4H), 5.12−5.22 (m, 2H), 5.96−5.97 (m, 1H). ^{13}C NMR (600 MHz, $CDCl_3$, 50 °C) δ 29.0, 29.1, 40.0, 40.1, 42.1, 53.7, 55.9, 73.0, 73.5, 78.0, 79.3, 82.0, 82.4, 118.0, 118.9, 134.2, 134.9, 155.2. MS (ESI-TOF): calcd for $C_{16}H_{26}N_2O_4Na^+$ (MNa^+), 333.1785; found, 333.1784.

Synthesis of *tert*-Butyl 1,2-Di(prop-2-ynyl)hydrazinecarboxylate 7: A solution of **5d** (400 mg, 1.30 mmol) in diphenyl ether (10 mL) was heated to 185 °C for 1.5 h. The crude mixture was subjected to flash chromatography using hexane (250 mL) and then ethyl acetate/hexane 1/16, compound **7** was isolated in 71% as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$, rt) δ 1.46 (s, 9H), 2.19−2.20 (m, 2H), 3.64 (m, 2H), 4.14 (s, 2H), 4.55 (bs, 1H). ^{13}C NMR (500 MHz, $CDCl_3$, rt) δ 28.2, 40.1, 71.2, 72.3, 79.5, 79.8, 81.8. MS (ESI-TOF): calcd for $C_{11}H_{16}N_2O_2Na^+$ (MNa^+), 231.1104; found, 231.1107. Mp 58.1−60.2 °C.

Synthesis of *tert*-Butyl 2-Methyl-1,2-di(prop-2-ynyl)hydrazinecarboxylate 8: To a solution of **7** (142 mg, 0.68 mmol) in DMF (8 mL) was added cesium carbonate (443 mg, 1.36 mmol) and methyl iodide (484 mg, 3.41 mmol). The mixture was stirred at room temperature for 3 days. The reaction mixture was diluted with water (30 mL) and extracted with dichloromethane (3 × 25 mL). The combined organic phases were washed with brine (3 × 25 mL), dried over magnesium sulfate, and concentrated in vacuo. Flash chromatography (ethyl acetate/hexane 1/30) yielded 50% of **8** as a colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$, rt) δ 1.46 (s, 9H), 2.18−2.20 (m, 2H), 2.78 (s, 3H), 3.74 (bs, 2H), 4.09 (bs, 1H). ^{13}C NMR (500 MHz, $CDCl_3$, rt) δ 28.6, 45.8, 71.1, 72.3, 80.27, 81.5. MS (ESI-TOF): calcd for $C_{12}H_{18}N_2O_2Na^+$ (MNa^+), 245.1260; found, 245.1257.

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Supporting Information Available: Experimental procedures and full spectroscopic details. This material is available free of charge via the Internet at http://pubs.acs.org.

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