Simple Preparation of Monoalkylhydrazines

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Abstract: Alkylation of *t*-butyl isopropylidene carbazate with alkyl bromides occurs under phase-transfer conditions. Acid hydrolysis of the product completes a simple two-step synthesis of monoalkylhydrazines.

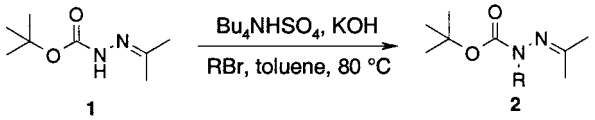
Key words: *t*-butyl carbazate, hydrazine, phase-transfer, alkylation, acid hydrolysis

tert-Butyl carbazate is a popular reagent for the preparation of substituted hydrazines. Protocols for the synthesis of aryl[1] and di- and tri-substituted[2] hydrazines from *tert*-butyl carbazate have recently appeared in the literature. Procedures for the formation of monoalkylhydrazines, important compounds in the synthesis of heterocycles containing an N-N bond,[3] from *tert*-butyl carbazate are also present in the literature, but are limited in scope. Venton et al.[4] reported formation of monoalkylhydrazines via condensation of *tert*-butyl carbazate with ketones or aldehydes followed by reduction with borane. This highly useful method provides access to hydrazines with secondary alkyl groups, but is limited to saturated ketones and aldehydes. Also, the alkyl group itself is derived from a ketone or aldehyde, limiting the hydrazines that can be prepared from commercially available reagents.

Alkylative methods have also been reported for the synthesis of monoalkylhydrazines. Zwierzak et al. have described phase-transfer conditions[5,6] for the alkylation of acetone *N*-(diethoxyphosphoryl)hydrazone with alkyl bromides, but the procedure requires large amounts of base, limiting the type of hydrazine that can be prepared, and often requires a multi-step synthesis of the hydrazone itself. In a recent report by Zwierzak et al.,[2a] alkylations of *tert*-butyl *iso*propylidene carbazate (**1**) with alkyl bromides are performed under anhydrous conditions with sodium hydride as the base. While high yields are obtained under these conditions, a milder, non-anhydrous procedure would enable the use of acid sensitive alkyl bromides and provide a safer alternative to sodium hydride for the large-scale preparation of monoalkylhydrazines.

It has been discovered that **1** can be alkylated under phase-transfer conditions using only a small excess of potassium hydroxide as base (Table 1). Despite the use of elevated temperatures (80 °C), the reaction conditions allow the use of base sensitive halides such as propargyl bromide (Table 1, **2e**), which could not be used under previous conditions.[5] Work-up consists only of washing the reaction mixture with water until a neutral pH is obtained, followed by removal of the toluene in vacuo. The reaction does not require anhydrous conditions and has been successfully used on a multi-gram scale.[7] The reaction is limited to the use of primary alkyl bromides as the alkylating agent, although activated (i.e. allyl, benzyl, etc.) alkyl chlorides have also been used successfully.[8]

Table 1 Alkylation of *t*-Butyl Carbazate Acetone Hydrazone

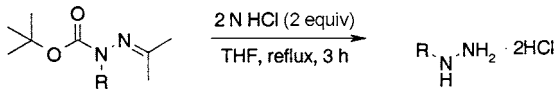


1 **2**

Product	R	Yield (%)[a]
2a	$CH_2CH_2CH_3$	84
2b	CH_2CH_2F	83
2c	$CH_2(c\text{-}C_3H_5)$	81
2d	$CH_2CH_2OCH_2CH_3$	77
2e	CH_2CCH	93
2f	$CH_2(C_6H_5)$	93

[a] Isolated yield.
[b] Determined by GC analysis.

Table 2 Hydrolysis of BOC Protected Hydrazones **2**



2 **3**

Product	R	Yield (%)[a]
3a	$CH_2CH_2CH_3$	73
3b	CH_2CH_2F	89
3c	$CH_2(c\text{-}C_3H_5)$	89
3d	$CH_2CH_2OCH_2CH_3$	95
3e	CH_2CCH	95
3f	$CH_2(C_6H_5)$	99

[a] Isolated yield prior to dilution and storage in EtOH.

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Hydrolysis of the hydrazone and removal of the BOC protecting group with two equivalents of aqueous HCl effectively liberate the monoalkylhydrazine (Table 2). After three hours the reaction is concentrated in vacuo and dried via azeotropic removal of water with toluene. The resulting salts were dissolved in ethanol and stored as stock solutions.[9]

In conclusion, a simple, robust procedure for the synthesis of monoalkylhydrazines has been described. The reaction is performed under non-anhydrous conditions using inexpensive, readily accessible reagents. The utilization of potassium hydroxide as the base presents a much safer alternative to sodium hydride. These benefits make this procedure the ideal method for both small- and large-scale production of monoalkylhydrazines and add to the breadth of synthetic methods of hydrazine preparation.

General Preparation of Alkylated Hydrazones (2): Solid KOH (powdered, 218 mg, 3.9 mmol) and tetrabutylammonium hydrogen sulfate (100 mg, 0.3 mmol) were added to a solution of *tert*-butyl *iso*propylidene carbazate (**1**)[10] (516 mg, 3.0 mmol) in toluene (10 mL). The mixture was stirred vigorously and heated to 50 °C whereupon neat alkyl bromide (3.6 mmol) was added slowly. The temperature was increased to 80 °C and maintained until the reaction was complete as indicated by GC-MS analysis (1–3 h). The mixture was cooled and washed with H_2O until the aqueous extract had a neutral pH. The organic layer was dried ($MgSO_4$) and concd in vacuo to give lightly colored oils (**2**),[11] which were used without further purification.

Monoalkylhydrazines (3): 2 N HCl (2 acid equiv) was added to a solution of **2** in THF (0.5 M) and heated for 3 h at reflux. The mixture was cooled and concd in vacuo. The residues were brought to complete dryness by addition and in vacuo removal of toluene (3 ×) and the yield was calculated. The resulting dihydrochloride salts[12] were diluted with EtOH, filtered through a filter disc (0.2 mm) to remove fine particles, and stored at ambient temperature in amber vials.

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(6) The alkylation conditions described in ref.[5] have also been used for N-alkylation of N-substitued carboxamides. See: Koziara, A.; Zawadzki, S.; Zwierzak, A. *Synth. Commun.* **1979**, 527.
(7) Hydrazine **3c** was prepared on 1 mol scale (68% overall yield) without any modification of the experimental procedure. In addition, a differential scanning calorimetry (DSC) test established compound **1** to be chemically stable in the temperature range described in the reaction conditions.
(8) Alkylations with allyl and benzyl chlorides were performed under identical conditions as those described for alkyl bromides with comparable yields and purities.
(9) The stock solutions of hydrazines have been stored in amber vials at room temperature for up to 1 year with no noticeable loss of molarity.
(10) **Experimental Procedure for the Preparation of *t*-Butyl Isopropylidene Carbazate (1):** Added $MgSO_4$ (ca. 2 g) and 5 drops of HOAc to a solution of *tert*-butyl carbazate (10 g, 75.6 mmol) in acetone (75 mL). The mixture was heated to reflux for 1 h then cooled, filtered and concd in vacuo to give 12.58 g (97%) of a white solid. Mp 85–87 °C.; lit. mp[2a] 85–87 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.46 (br s, 1 H), 1.97 (s, 3 H), 1.77 (s, 3 H), 1.45 (s, 9 H). ^{13}C NMR (300 MHz, $CDCl_3$): δ = 16.1, 25.5, 28.4, 81.0, 150.0, 153.1.
(11) **2a (R = *n*-propyl)**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.45 (t, *J* = 7.4 Hz, 2 H), 2.06 (s, 3 H), 1.86 (s, 3 H), 1.48 (m, 2 H), 1.44 (s, 9 H), 0.88 (t, *J* = 7.4 Hz, 3 H). **2b (R = 2-fluoroethyl)**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.56 (t, *J* = 5.1 Hz, 1 H), 4.40 (t, *J* = 5.1 Hz, 1 H), 3.86 (t, *J* = 5.1 Hz, 1 H), 3.78 (t, *J* = 5.1 Hz, 1 H), 2.07 (s, 3 H), 1.90 (s, 3 H), 1.46 (s, 9 H). **2c (R = cyclopropylmethyl)**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.36 (d, *J* = 6.9 Hz, 2 H), 2.08 (s, 3 H), 1.91 (s, 3 H), 1.45 (s, 9 H), 0.96 (m, 1 H), 0.43 (m, 2 H), 0.20 (m, 2 H). **2d (R = 2-ethoxyethyl)**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.69 (t, *J* = 6.3 Hz, 2 H), 3.48 (m, 4 H), 2.06 (s, 3 H), 1.88 (s, 3 H), 1.45 (s, 9 H), 1.16 (t, *J* = 7.1 Hz, 3 H). **2e (R = 3-propynyl)**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.24 (d, *J* = 2.3 Hz, 2 H), 2.18 (t, *J* = 2.3 Hz, 1 H), 2.10 (s, 3 H), 1.92 (s, 3 H), 1.46 (s, 9 H). **2f (R = benzyl)**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.29 (m, 5 H), 4.68 (s, 2 H), 2.03 (s, 3 H), 1.70 (s, 3 H), 1.45 (s, 9 H).
(12) **3a (R = *n*-propyl)**: ^{1}H NMR (300 MHz, d_6-DMSO): δ = 2.84 (t, *J* = 7.7 Hz, 2 H), 1.57 (m, 2 H), 0.88 (t, *J* = 7.5 Hz, 3 H). ^{13}C NMR (300 MHz, d_6-DMSO): δ = 11.1, 18.1, 52.2. **3b (R = 2-fluoroethyl)**: ^{1}H NMR (300 MHz, d_6-DMSO): δ = 4.60 (dt, *J* = 47.2, 4.7 Hz, 2 H), 3.19 (dt, *J* = 28.0, 4.7 Hz, 2 H). ^{13}C NMR (300 MHz, d_6-DMSO): δ = 49.6 (d, *J* = 20 Hz), 80.5 (d, *J* = 166 Hz). **3c (R = cyclopropylmethyl)**: ^{1}H NMR (300 MHz, d_6-DMSO): δ = 2.78 (d, *J* = 7.5 Hz, 2 H), 1.01 (m, 1 H), 0.52 (m, 2 H), 0.31 (m, 2 H). ^{13}C NMR (300 MHz, d_6-DMSO): δ = 3.7, 6.4, 55.3. **3d (R = 2-ethoxyethyl)**: ^{1}H NMR (300 MHz, d_6-DMSO): δ = 3.56 (t, *J* = 5.5 Hz, 2 H), 3.45 (q, *J* = 7.0 Hz, 2 H), 3.05 (t, *J* = 5.5 Hz, 2 H), 1.12 (t, *J* = 7.0 Hz, 3 H). ^{13}C NMR (300 MHz, d_6-DMSO): δ = 15.0, 49.6, 65.7. **3e (R = 3-propynyl)**: ^{1}H NMR (300 MHz, d_6-DMSO): δ = 3.68 (d, *J* = 2.4 Hz, 2 H), 3.40 (t, *J* = 2.4 Hz, 1 H). ^{13}C NMR (300 MHz, d_6-DMSO): δ = 39.1, 77.6, 78.8. **3f (R = benzyl)**: ^{1}H NMR (300 MHz, d_6-DMSO): δ = 7.45–7.30 (m, 5 H), 4.06 (s, 2 H). ^{13}C NMR (300 MHz, d_6-DMSO): δ = 54.3, 128.8, 129.1, 130.1, 134.6.