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Simple Approach to 1-Alkyl-2-isopropylhydrazines

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Ditosylates of 1-alkyl-2-isopropylhydrazines were prepared by *N*-alkylation of *t*-butyl isopropylidenecarbazate (**2**) followed by reduction of *N*-alkyl-*t*-butyl isopropylidenecarbazate (**3**) with lithium aluminum hydride in boiling tetrahydrofuran. The removal of *N*-Boc protecting group was quantitatively achieved by refluxing *N*-alkyl-*t*-butyl isopropylcarbazate (**4**) with p-toluenesulfonic acid monohydrate in dichloromethane.

Key words: *t*-butyl carbazate (*N*-Boc hydrazide), alkylation, LAH reduction, Boc removal

Some symmetrically substituted hydrazines exhibit biological activity as marked tumour inhibitors [1,2], but their mode of action has not been fully elucidated [3]. 1,2-Dialkylhydrazines have also attracted considerable interest as starting materials for the preparation of some heterocyclic systems and azoalkanes – useful progenitors of alkyl radicals by photolytic, radiolytic, and pyrolytic reactions [4].

RESULTS AND DISCUSSION

Symmetrically substituted hydrazines are typically prepared by reduction of 1-acyl-2-alkylidenehydrazines (acylhydrazones) with lithium aluminum hydride [4,5]. The procedure is, however, tedious and usually gives a low overall yield of impure final product. Alternative reduction of aldehyde alkylhydrazones with diborane [6] is operationally inconvenient and demands the use of not readily accessible alkylhydrazines as starting materials. The method described by us [7] is generally applicable only to 1,2-dialkylhydrazines, substituted with primary alkyl groups on both nitrogens. Only a few examples of 1-alkyl-2-isopropylhydrazines have been reported [4–6] but except 1-benzyl-2-isopropylhydrazine [6] without satisfactory proof of purity and homogeneity.

We have found that commercially available *t*-butyl carbazate (**1**) can be a convenient starting material for the preparation of doubly substituted 1,2-dialkylhydrazines, in which the alkyl groups are not identical. On refluxing with acetone **1** could be transformed quantitatively into *t*-butyl isopropylidenecarbazate (**2**). Metalation of **2** with sodium hydride in tetrahydrofuran, followed by *N*-alkylation by means of pri-

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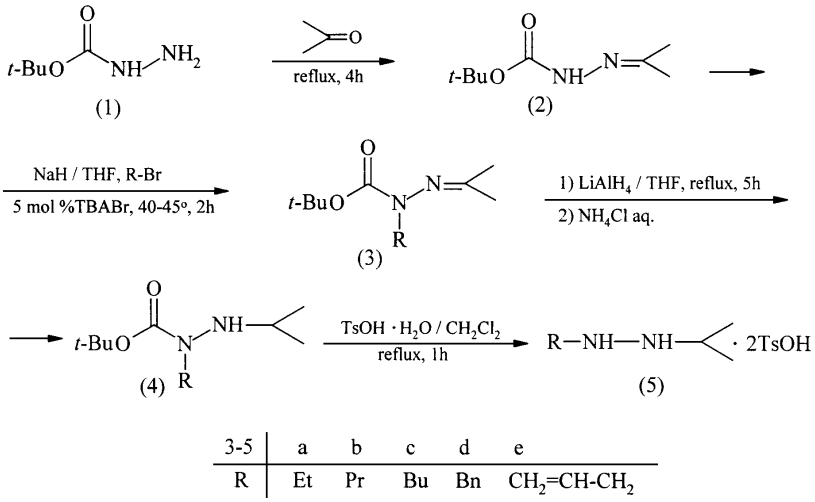
mary alkyl bromides in the presence of 5 mol % of tetrabutylammonium bromide (TBABr) as catalyst, proceeded smoothly at 40–45° to afford the corresponding *N*-alkyl-*t*-butyl isopropylidenecarbazate (**3**) in high yield and spectroscopic purity. Crude **3** could be used directly for reduction with lithium aluminum hydride without purification.

Scheme



3-5	a	b	c	d	e
R	Et	Pr	Bu	Bn	CH_2=CH-CH_2

The reduction of **3** was performed in refluxing tetrahydrofuran, using 50% excess of lithium aluminum hydride. Yields and spectroscopic data of *N*-alkyl-*t*-butyl isopropylidenecarbazate (**3**) and *N*-alkyl-*t*-butyl isopropylcarbazate (**4**) are compiled in Table 1. Crude **4** were easily and cleanly deprotected by refluxing with two equivalents of p-toluenesulfonic acid monohydrate in dichloromethane to give quantitative yields of 1-alkyl-2-isopropylhydrazine ditosylates (**5**) as crystalline solids. Analytically pure samples of **5** were obtained by crystallization from ethyl acetate. Yields, melting points and spectroscopic data of ditosylates (**5**) are summarized in Table 2.

N-Alkyl-*t*-butyl isopropylidenecarbazates (**3**) could be also effectively employed for the preparation of monoalkylhydrazine tosylates (**6a,b**) by simultaneous removal of hydrazone residue and *N*-Boc group with p-toluenesulfonic acid monohydrate in refluxing aqueous ethanol. The reported procedures supplement the existing repertoire of synthetic methods leading to alkylhydrazines.

EXPERIMENTAL

All solvents and reagents were purchased from Fluka. Melting points (determined in open capillary tubes) are uncorrected. IR spectra (KBr discs) were measured using a Specord M 80 (C. Zeiss) instrument. ^{1}H NMR spectra were recorded on a Bruker AVANCE DPX-250 spectrometer operating at 250 MHz using

Table 1. *N*-Alkyl-*t*-butyl isopropylidenecarbazates (**3**) and *N*-alkyl-*t*-butyl isopropylcarbazates (**4**).

Compound No.	Yield[a] %	^{1}H NMR ($CDCl_3$)[b] δ, ppm J, Hz
3a	93	1.12 (t, 3H, J = 7.1); 1.46 (s, 9H); 1.87 (s, 3H); 2.08 (s, 3H); 3.53 (q, 2H, J = 7.1)
3b	80	0.89 (t, 3H, J = 7.5); 1.46 (s, 9H); 1.43–1.64 (m, 2H); 1.87 (s, 3H); 2.07 (s, 3H); 3.46 (t, 2H, J = 7.3)
3c	86	0.92 (t, 3H, J = 7.5); 1.26–1.37 (m, 2H); 1.45 (s, 9H); 1.40–1.56 (m, 2H); 1.86 (s, 3H); 2.07 (s, 3H); 3.49 (t, 2H, J = 7.5)
3d	95	1.45 (s, 9H); 1.70 (s, 3H); 2.00 (s, 3H); 4.67 (s, 2H); 7.18–7.36 (m, 5H)
3e	79	1.46 (s, 9H); 1.88 (s, 3H); 2.06 (s, 3H); 4.08 (bd, 2H, J = 6.0); 5.08–5.25 (m, 2H); 5.78–5.95 (m, 1H)
4a	70	1.01 (d, 6H, J = 6.6); 1.10 (t, 3H, J = 7.0); 1.48 (s, 9H); 3.17 (bsp, 1H, J = 6.6); 3.37 (q, 4H, J = 7.0)
4b	70	0.85 (t, 3H, J = 7.5); 1.01 (d, 6H, J = 6.3); 1.47 (s, 9H); 1.58 (sx, 2H, J = 7.5); 3.18 (sp, 1H, J = 6.3); 3.28 (bt, 2H, J = 7.5)
4c	82	0.91 (t, 3H, J = 7.5); 1.01 (d, 6H, J = 6.3); 1.18–1.35 (m, 2H); 1.47 (s, 9H); 1.51 (qt, 2H, J = 7.5); 3.18 (sp, 1H, J = 6.3); 3.31 (bt, 2H, J = 7.3)
4d	74	1.01 (d, 6H, J = 6.3); 1.46 (s, 9H); 3.22 (sp, 1H, J = 6.3); 4.41 (s, 2H); 7.10–7.40 (m, 5H)
4e	69	1.02 (d, 6H, J = 6.6); 1.47 (s, 9H); 3.18 (sp, 1H, J = 6.5); 3.95 (bd, 2H, J = 5.5); 5.04–5.16 (m, 2H); 5.75–5.90 (m, 1H)

[a]Yields of crude compounds (**3**) and (**4**).
[b]Abbreviations used: s, singlet; d, doublet; t, triplet; q, quartet; qt, quintet; sx, sextet; sp, septet; m, multiplet; b, broad.

Table 2. 1-Alkyl-2-isipropylhydrazine ditosylates (**5**).

Compound No.	M.p. °C	^{1}H NMR ($CDCl_3$)[a] δ, ppm J, Hz	IR (KBr) ν cm^{-1}	FAB/MS[b]
5a	137–139	1.13 (t, 3H, J = 7.5); 1.22 (d, 6H, J = 7.5); 2.31 (s, 6H); 3.14 (q, 2H, J = 7.5); 3.41 (sp, 1H, J = 7.5); 7.10 (bs, 4H); 7.00–7.73 (AA′XX′ system, 4H)	2800–2100, 1500, 1255, 1115, 1040, 1005, 820, 690, 570	103 (M-2TsO-1)
5b	99–101	0.83 (t, 3H, J = 7.5); 1.31 (d, 6H, J = 6.5); 1.59 (sx, 2H, J = 7.5); 2.36 (s, 6H); 3.13 (bt, 2H, J = 7.5); 3.60 (sp, 1H, J = 6.5); 7.10–7.80 (AA′XX′ system, 4H); 9.17 (bs, 4H)	3100–2200, 1500, 1240, 1160, 1135, 1040, 1010, 820, 690, 570	117 (M-2TsO-1)
5c	100–101	0.81 (t, 3H, J = 7.3); 1.26 (sx, 2H, J = 7.5); 1.33 (d, 6H, J = 6.5); 1.53 (qt, 2H, J = 7.5); 2.37 (s, 6H); 3.17 (bt, 2H, J = 7.5); 3.61 (sp, 1H, J = 6.5); 7.10–7.75 (AA′XX′ system, 4H); 8.22 (bs, 4H)	2760–2100, 1600, 1500, 1250, 1135, 1040, 1005, 815, 690, 570	131 (M-2TsO-1)
5d	112–114	1.34 (d, 6H, J = 6.5); 2.37 (s, 6H); 3.49 (sp, 1H, J = 6.5); 4.25 (s, 2H); 7.15–7.75 (AA′XX′ system, 4H); 8.63 (bs, 4H)	2740–2100, 1600, 1500, 1250, 1130, 1040, 1000, 815, 685, 570	165 (M-2TsO-1)
5e	98–99	1.33 (d, 2H, J = 6.5); 2.37 (s, 6H); 3.53 (sp, 1H, J = 6.5); 3.75 (bd, 2H, J = 6.4); 5.20–5.37 (m, 2H); 5.72–5.90 (m, 1H); 7.15–7.75 (AA′XX′ system, 4H); 8.50 (bs, 4H)	2700–2100, 1602, 1500, 1245, 1130, 1100, 1040, 1000, 810, 680, 570	115 (M-2TsO-1)

[a]Abbreviations used: s, singlet; d, doublet; t, triplet; q, quartet; qt, quintet; sx, sextet; sp, septet; m, multiplet; b, broad.
[b]All compounds 5 have been satisfactorily analysed (C ± 0.2%, H ± 0.25%, N ± 0.1%).

$CDCl_3$ solutions. FAB/MS were measured on an APO Electron (Ukraine) Model MI 1200 IE mass spectrometer equipped with a FAB source (thioglycerol matrix).

Preparation of *t*-butyl isopropylidenecarbazate (2): A solution of *t*-butyl carbazate (**1**, 5.28 g, 0.04 mol) in acetone (30 ml) was refluxed for 4 h. Evaporation of solvent left 6.88 g (100%) of analytically pure **2** as colourless, crystalline solid, m.p. 85–87°C; ^{1}H NMR ($CDCl_3$) δ: 1.51 (s, 9H), 1.81 (s, 3H), 2.04 (s, 3H), 7.36 (bs, 1H); IR: ν_{max} (KBr) 3256, 1724, 1710, 1536, 1368, 1284, 1248, 1152, 1056 cm^{-1}. Anal. Calcd for $C_8H_{16}N_2O_2$: C, 55.8; H, 9.4. Found: C, 56.0; H, 9.3.

Preparation of *N*-alkyl-*t*-butyl isopropylidenecarbazates (3a–e). General procedure: Sodium hydride (0.48 g of 50% suspension in mineral oil, 0.01 mol) was added portionwise with stirring to the solution of *t*-butyl isopropylidenecarbazate (**2**, 1.72 g, 0.01 mol) and tetrabutylammonium bromide (TBABr, 0.161 g, 5 mol %) in THF (30 ml). After *ca.* 10 min a solution of alkyl bromide (0.011 mol) in THF (5 ml) was added dropwise and stirring was continued at 40–45°C for 2 h. The resultant mixture was filtered and evaporated. The residue was dissolved in CH_2Cl_2 (50 ml), washed with water (2 × 15 ml), dried, and evaporated *in vacuo* to give *N*-alkyl-*t*-butyl isopropylidenecarbazates (**3a–e**) as colourless oils. Yields and ^{1}H NMR data of crude **3** are compiled in Table 1.

Preparation of *N*-alkyl-*t*-butyl isopropylcarbazates (4a–e). General procedure: A solution of crude *N*-alkyl-*t*-butyl isopropylidenecarbazate (**3**, 0.010 mol) in THF (10 ml) was added dropwise with stirring to the suspension of lithium aluminum hydride (0.569 g, 0.015 mol) in THF (30 ml). The mixture was refluxed for 5 h, cooled to room temp., diluted with ethyl acetate (20 ml), and quenched with saturated aqueous NH_4Cl solution at +5°C. The organic layer was separated. The aqueous phase was extracted with ether (20 ml) and combined organic solutions were dried over $MgSO_4$ and evaporated *in vacuo* to give spectroscopically pure (^{1}H NMR) **4a–e** as colourless oils. Yields and ^{1}H NMR data of crude **4** are compiled in Table 1.

Deprotection of 4. Preparation of 1-alkyl-2-isopropylhydrazine ditosylates (5a–e). General procedure: A solution of p-toluenesulfonic acid monohydrate (1.90 g, 0.01 mol) in minimal amount of EtOH was added to the solution of crude **4** (0.005 mol) in CH_2Cl_2 (15 ml) and the mixture was refluxed gently for 1 h. Evaporation of solvent *in vacuo* left quantitative amounts of **5** as colourless, crystalline solids. Crude **5** were recrystallized from ethyl acetate. Yields, m.p.`s. and spectroscopic data of pure ditosylates (**5a–e**) are summarized in the Table 2.

Preparation of ethylhydrazine p-toluenesulfonate (6a). The mixture of *N*-ethyl-*t*-butyl isopropylidenecarbazate (**3a,** 0.008 mol), p-toluenesulfonic acid monohydrate (0.008 mol), EtOH (15 ml), and water (0.15 ml) was refluxed gently for 6 h. Quantitative yield of crude **6a** was obtained on evaporation of solvent. Crystallization from ethanol-ether afforded pure tosylate, m.p. 89–91°C (lit. [8] m.p. 122–124°C); ^{1}H NMR ($CDCl_3$) δ: 1.16 (t, 3H, J = 7.5 Hz), 2.35 (s, 3H), 3.09 (q, 2H, J = 7.5 Hz), 6.23 (bs, 4H), 7.12–7.80 (AA′XX′ system, 4H); IR: ν_{max} (KBr) 3350, 3200–2700, 1620, 1210, 1160, 1130, 1040, 1010, 820, 685, 570 cm^{-1}. Anal. calcd for $C_9H_{16}N_2O_3S$: C, 46.5; H, 6.9. Found : C, 46.6; H, 6.8.

Preparation of butylhydrazine p-toluenesulfonate (6b). The compound was obtained in quantitative yield as described above. M.p. 115–116°C (lit. [8] m.p. 116–118°C); ^{1}H NMR ($CDCl_3$) δ: 0.78 (t, 3H, J = 7.5 Hz), 1.21 (sextet, 2H, J = 7.5 Hz), 1.54 (qt, 2H, J = 7.5 Hz), 2.36 (s, 3H), 3.00 (t, 2H, J = 7.5Hz), 6.44 (bs, 4H), 7.14–7.78 (AA′XX′system, 4H).

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