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New entry to alicyclic amines via alkylative fragmentation of cyclic aminoaldehyde tosylhydrazones†

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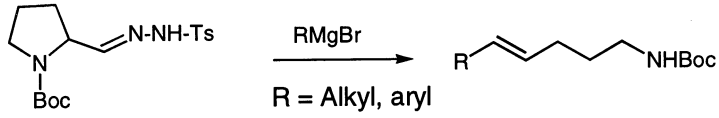
Abstract

Tosylhydrazones of cyclic aminoaldehydes when exposed to aromatic and aliphatic Grignard reagents produce ring-opened acyclic unsaturated primary carbamates and carbamate alcohols in good yields.

Keywords: *p*-toluenesulfonyl hydrazine; amine; proline; hydroxyproline.

Amines and amino alcohols containing an alkene double bond are very important building blocks in organic synthesis.[1] This class of compounds have multiple functionality for further manipulation towards the synthesis of natural products and designed pharmaceutically valuable compounds.[2] Our group has been engaged in the development of this class of compounds over the past few years.[3] As part of an ongoing project[4] on the exploitation of our newly discovered methodology on alkylative fragmentation of aldehyde tosylhydrazones having α-heteroatom functionality, we have observed that both five- and six-membered nitrogen heterocycles with the aldehyde tosylhydrazone functionality at C_2 undergo alkylative fragmentation to result in acyclic amines and aminols having unsaturation (between C_4–C_5 or C_5–C_6). The results pertaining to this study are reported herein (Eq. (1)).



(1)

Initially, pyrrolidine-2-carboxaldehyde was protected with di-*tert*-butyl dicarbonate and derivatized with *p*-toluenesulfonyl hydrazine to afford the prerequisite hydrazone **1** (entry 1, Table 1). This was subjected to phenyl magnesium bromide (2.5 equiv.) in anhydrous THF for

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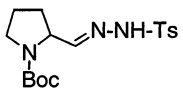
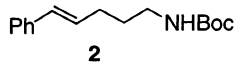
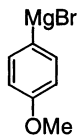
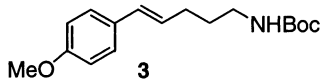
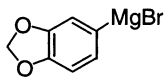
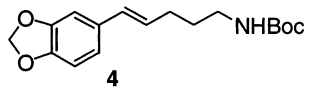
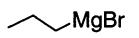
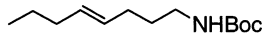
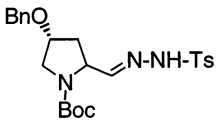
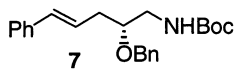
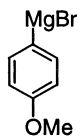
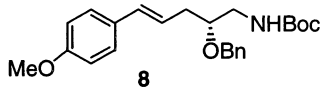
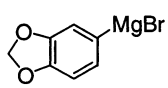
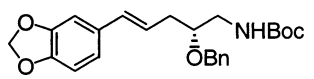
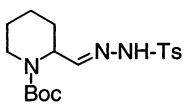
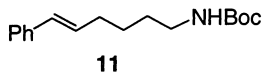
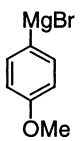
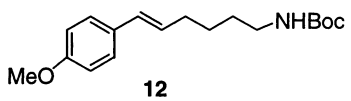
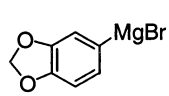
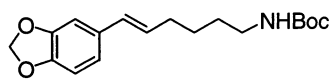
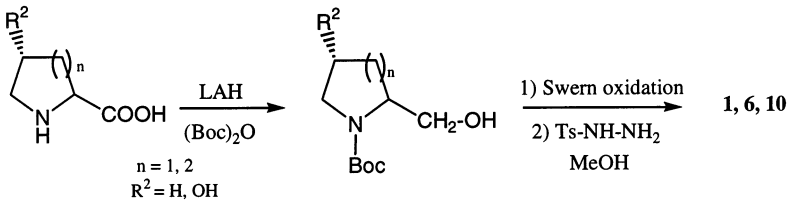
4 h to afford 5-phenyl-4-pentenyl amine derivative[5] **2** in 75% yield. However, when the same reaction was carried out with unprotected pyrrolidine hydrazone, a complex and an uncharacterizable mixture of products was obtained. Thus, it is anticipated that the acidic N–H is better off being protected (Eq. (2), Scheme 1).

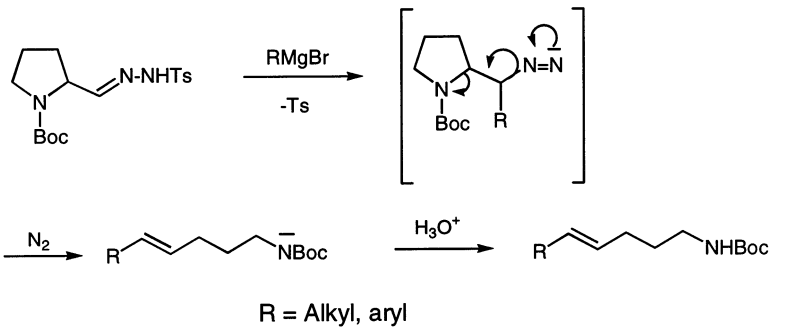
Table 1

Entry	Substrate	Reagent	Product[a]	Yields(%)[b]
1	 **1**	PhMgBr	 **2**	75
2			 **3**	65
3			 **4**	72
4			 **5**	65
5	 **6**	PhMgBr	 **7**	60
6			 **8**	65
7			 **9**	72
8	 **10**	PhMgBr	 **11**	70
9			 **12**	75
10			 **13**	72

a) The olefin geometry of alicyclic carbamates found to be *trans* by spectroscopic analysis (except entry 4 compound **5**, E/Z, 90:10)
b) Yields calculated after column chromatography of the products



Scheme 1.



(2)

To check generality of this method, **1** was subjected to 4-methoxyphenylmagnesium bromide under identical reaction conditions to give Boc-protected 4-methoxyphenyl-pentenyl amine in 65% yield. Hydrazone **1** was also treated with 3,4-methylenedioxy phenylmagnesium bromide and propylmagnesium bromide to provide ring-opened products in moderate yields (entry 3 and 4). The tosylhydrazone **6**, which is obtained from 4-hydroxyproline, when exposed to PhMgBr, 4-MeO-PhMgBr, and 3,4 methylenedioxyphenylmagnesium bromide gave the corresponding amino alcohols (**7**, **8**, **9**).[6] Identical results were drawn from tosylhydrazone **10** (entry 8, Table 1) to afford the ring-opened acyclic amines having unsaturation between C_5–C_6 (entries 8, 9, 10).

In conclusion, a facile and convenient method for the synthesis of double bond containing terminal carbamates and carbamate alcohols has been developed, which should find use in organic synthesis.

Acknowledgements

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Goodman, L. S.; Gillman, A., Eds.; McMillan: New York, 1980. (d) McCarty, F. J. Rosenstock, P. D.; Paolini, J. P.; Micucel, D. D.; Ashton, L.; Benneetts, W. W.; Palopoli, F. P. *J. Med. Chem.* **1968**, *11*, 534.

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5. General procedure: Preformed arylmagnesium bromide (2.5 mmol) in (15 mL) anhydrous THF was added dropwise to a cold aminoaldehyde *p*-toluenesulfonyl hydrazone (1 mmol) in (5 mL) anhydrous THF under a nitrogen atm, then stirred at ambient temperature for 4 h. The reaction mixture was quenched with saturated NH_4Cl solution (10 mL) and extracted with ether (2×25 mL). The combined organic layers were washed with water, brine and dried over Na_2SO_4. The volatiles were removed under vacuum and the residue was purified by column chromatography to afford *trans*-Boc-protected compounds (see Table 1).
6. Spectroscopic data of compounds: compound **2**. ^1H NMR $CDCl_3$ 200 MHz: δ 7.4–7.15 (m, 5H), 6.40 (d, 1H, $J=15$ Hz), 6.25–6.10 (m, 1H), 4.50 (bs, 1H), 3.25–3.15 (m, 2H), 2.35–2.20 (m, 2H), 1.75–1.6 (m, 2H), 1.45 (s, 9H); IR (neat): 3325, 1687, 1280, 1150 cm^{-1}; EI MS: m/z 205 (M^+-56), 144, 105, 77, 57: compound **7**. ^1H NMR $CDCl_3$ 200 MHz: δ 7.40–7.20 (m, 10H), 6.55 (d, 1H, $J=15$ Hz), 5.80–5.65 (m, 1H), 4.80 (bs, 1H), 4.70–4.65 (m, 1H), 4.62–4.50 (dd, 2H, $J=9.6$, 19.2 Hz), 3.62–3.05 (m, 2H), 2.72–2.45 (m, 2H), 1.45 (s, 9H); IR (neat): 3306, 1685, 1282, 1103 cm^{-1}; EI MS: m/z 311 (M^+-56) 204, 107, 57: compound **12**. ^1H NMR $CDCl_3$ 200 MHz: δ 7.25 (d, 2H, $J=8.3$ Hz), 6.80 (d, 2H, $J=8.3$ Hz), 6.30 (d, 1H, $J=16$ Hz), 6.10–5.95 (m, 1H), 4.50 (bs, 1H), 3.80 (s, 3H), 3.10–2.90 (m, 2H), 2.30–2.10 (m, 2H), 2.0–1.65 (m, 4H), 1.45 (s, 9H). IR (neat): 3320, 1685, 1280, 1175 cm^{-1}; EI MS: m/z 249 (M^+-56), 188, 147, 121, 57.