Direct Conversion of Tosylhydrazones to *tert*-Butyl Ethers under Bamford-Stevens Reaction Conditions[1]

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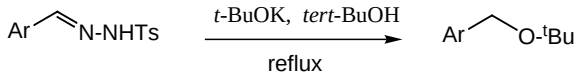
Abstract: A new method for the preparation of *tert*-butyl ethers is described starting from aryl aldehyde and ketone tosylhydrazones under Bamford-Stevens reaction conditions (*t*-BuOK/ *t*-BuOH).

Key words: tosylhydrazones, *tert*-butyl ethers, potassium *tert*-butoxide, *tert*-butanol, diazocompounds

Introduction of *tert*-butyl ether functionality into existing organic molecule tends to change not only the physical but also chemical and biological properties of the parent molecule. For example the alkyl *tert*-butyl ethers are considered as possible gasoline additives due to their high energy content and high octane number.[2] Also the bulk of *tert*-butyl group efficiently impedes any chelation of the metal by the oxygen of *tert*-butyl ether functionality. Occasional reports also show that the *tert*-butyl functionality has profound effect on biological profile as exemplified by several bioactive molecules in SAR studies.[3]

As part of ongoing project on the exploitation of aldehyde tosylhydrazone chemistry,[4] especially the thiophene 2-aldehyde tosylhydrazone,[4e] we have serendipitously observed the formation of *tert*-butyl ether (Scheme 1) when the thiophene 2-aldehyde tosylhydrazone was treated with *t*-BuOK in *t*-BuOH (analogous to Bamford-Stevens reaction[5] conditions).



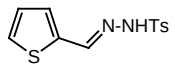
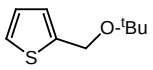
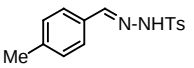
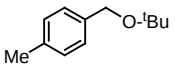
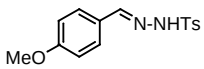
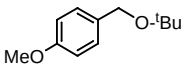
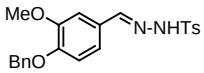
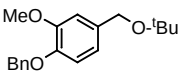
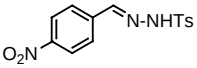
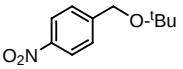
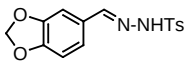
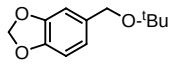
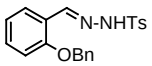
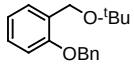
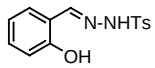
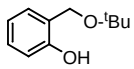
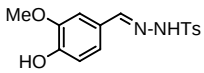
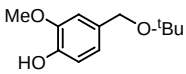
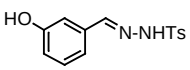
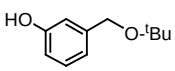
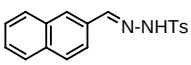
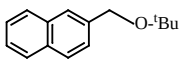
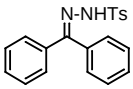
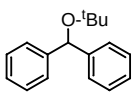
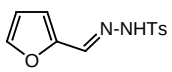
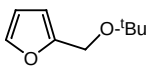
Ar = heterocycle, substituted phenyl

Scheme 1

This result prompted us to look into the reaction pathway and also generalize the protocol. The results pertaining to this new observation are documented herein (Table). There are some protocols, which describe the synthesis of *tert*-butyl ethers[6] and few involving photolysis.[7]

Mechanistically it is anticipated that, in the presence of protic solvent, the formed diazo intermediate[8] abstracts a proton to give the diazonium ion, which loses N_2 to give the corresponding carbocation (Bamford-Stevens mecha-

Table Direct Conversion of Tosylhydrazones to *tert*-Butyl Ethers

Entry	Substrate	Product[b]	Yields[a] (%)
1			82
2			85
3			86
4			85
5			78
6			80
7			79
8			76
9			78
10			74
11			81
12			79
13			83

[a] Yields were calculated after purification by column chromatography.
[b] All the products were characterized by ^{1}H NMR, IR and mass spectroscopy.

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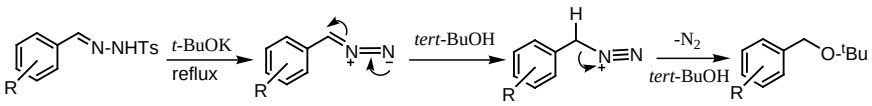

R = alkyl, *o*-alkyl, hydroxy

Scheme 2

nism) which may not undergo elimination due to the absence of α-hydrogen and hence leading to desired *tert*-butyl ether in the presence of *t*-BuOH (Scheme 2).

To further strengthen the above hypothesis, *p*-tolualdehyde tosylhydrazone (entry 2) was treated under similar reaction conditions to isolate 4-methyl benzyl *tert*-butyl ether in 85% yield. Similar results were observed for *p*-methoxy benzaldehyde tosylhydrazone (entry 3), 4-benzyloxy-3-methoxy benzaldehyde tosylhydrazone (entry 4), naphthaldehyde tosylhydrazone (entry 11) and furfuraldehyde tosylhydrazone (entry 12). Also methylenedioxy derivative (entry 6) and *o*-benzyloxy substrate (entry 7) yielded the targeted *tert*-butyl ethers in 80% and 85% yields respectively. The salcilaldehyde tosylhydrazone (entry 8) yielded the *o*-hydroxy benzyl *tert*-butyl ether (78% yield). Thus this example demonstrates that one would prepare the *tert*-butyl ether of benzyl alcohol in presence of phenolic functionality without protection. This result is further demonstrated by the preparation of 3-hydroxy-4-methoxy benzyl *tert*-butyl ether (entry 9) and 3-hydroxy benzyl *tert*-butyl ether (entry 10). Entry 12 demonstrates the formation of very hindered 1,1-diphenyl methyl *tert*-butyl ether in 76% yield. *p*-Nitro benzaldehyde tosylhydrazone (entry 5) resulted in the corresponding *tert*-butyl ether in 78% yield.

In conclusion, it is demonstrated that aryl aldehydes and ketones can be converted to corresponding *tert*-butyl ethers *via* tosylhydrazones. Further studies to modify the present protocol and its applications are being pursued actively.

General Procedure

To the stirred solution of potassium *tert*-butoxide (1.2 mmol)[9] in *t*-BuOH was added arylaldehyde tosylhydrazone (1 mmol) at 0 °C and allowed to stir for 10 minutes. The reaction mixture was refluxed for 4 hours and cooled to room temperature. *t*-BuOH was removed under vacuum and residue was extracted with ethylacetate (3 × 20 mL), washed with water, brine and dried over sodium sulfate and purified by column chromatography to afford the pure product.[10]

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(9) For free hydroxy aldehyde tosylhydrazones (entries 8–10), *t*-KOBu (2.4 mmol)was used. After completion, the reaction mixture was acidified with saturated sodium bisulfate.
(10) Spectral data of products: **1-** ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.22 (m, 1 H), 6.94 (m, 2 H), 4.58 (s, 2 H), 1.22 (s, 9 H). IR (KBr): 2982, 1574, 1054 cm^{-1}. EI MS *m/z*; 170 (M^+), 114, 97. **6-** ^{1}H NMR (200 MHz, $CDCl_3$)δ 6.82 (s, 1 H), 6.70 (m, 2 H), 5.90 (s, 2 H), 4.32 (s, 2 H), 1.26 (s, 9 H). IR (KBr): 2972, 1568, 1020 cm^{-1}. EIMS *m/z*; 208 (M^+), 152, 135. **12-** ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.20 (m, 10 H), 5.51 (s, 1 H), 1.21 (s, 9 H). IR (KBr): 2986, 1590, 1048 cm^{-1}. EIMS *m/z*; 240 (M^+), 184, 167, 107.