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Acid-catalyzed N-alkylation of tosylhydrazones using benzylic alcohols

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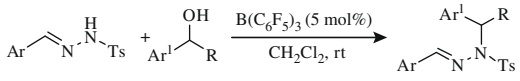
ABSTRACT

N-Alkylation of tosylhydrazones in the presence of an acid catalyst is described for the first time. Tris(pentafluorophenyl) borane was found to be a mild and efficient catalyst when benzylic alcohols were used as the alkylating agents.

In continuation of our earlier work in the alkylation of various compounds such as sulfonamides[1] and coumarins[2] under acid catalysis using benzylic alcohols, we were interested in exploring the N-alkylation of tosylhydrazones. A careful literature survey revealed that there is no precedent for the acid-catalyzed N-alkylation of tosylhydrazones. Commonly, N-alkylation is achieved using alkyl halide/base[3] and in the presence of phase transfer catalyst.[4] Recently, N-alkylation of tosylhydrazones was achieved using alcohols under Mitsunobu reaction conditions (DEAD/Ph_3P).[5] Furthermore, these N-alkylated hydrazones have various applications in organic synthesis as useful synthons.[6] Reductive deoxygenation of alcohols can also be achieved via N-alkylation of hydrazones.[7] Thus, the development of new methods for N-alkylation of tosylhydrazones is of significance.

In the light of above comments, herein we wish to report the results on N-alkylation of tosylhydrazones using benzylic alcohols as alkylating agents under acidic conditions (Scheme 1).

Initially, the reaction of *N′*-benzylidene-4-methylbenzene sulfonohydrazide (**1a**) with diphenyl methanol (**2a**) was carried out in dichloromethane using *p*-toluenesulfonic acid (5 mol %) at room temperature for 30 h, under which conditions the N-alkylation reaction took place. However, this afforded the desired product, *N*-benzhydryl-*N′*-benzylidene-4-methylbenzenesulfonohy drazide (**3a**) in only 45% yield (Table 1, entry 1). When, the same reaction was conducted at reflux temperature for 24 h, there was no improvement in the yield (Table 1, entry 2). Based on these results, the same reaction was screened with different acid catalysts (5 mol %) to find the best



Ar = aryl
Ar^1 = aryl; R = aryl, alkyl, H

Scheme 1. N-alkylation of tosylhydrazones.

Table 1
Acid-catalyzed N-alkylation of tosyl hydrazone **1a** with alcohol **2a** using acid catalysts

Entry	Acid (5 mol %)	Conditions	Time (h)	Yield[a] (%)
1	*p*-TSA	CH_2Cl_2/rt	30	45
2	*p*-TSA	CH_2Cl_2/reflux	24	48
3	$B(C_6F_5)_3$	CH_2Cl_2/rt	20	90
4	BF_3Et_2O	CH_2Cl_2/rt	24	46
5	$ZnCl_2$	CH_2Cl_2/rt	24	44
6[c]	PS-*p*TSA	CH_2Cl_2/reflux	24	0[b]
7[c]	PS-*p*TSA	CH_3NO_2/reflux	20	85[d]

[a] Isolated yield after purification.
[b] No reaction.
[c] 50 mg/mmol catalyst used.
[d] No reaction at rt.

catalyst for N-alkylation (Table 1). Among the catalysts screened tris(pentafluorophenyl) borane [$B(C_6F_5)_3$] gave good yields of the N-alkylated product (Table 1, entry 3), whereas, $ZnCl_2$ and $BF_3{\cdot}Et_2O$ furnished the product in low yields (Table 1, entries 4 and 5). However, polystyrene-bound *p*-TSA (50 mg/mmol) in nitromethane under refluxing conditions provided the product **3a** in good yields (Table 1, entry 7), while there was no reaction either at room temperature or in dichloromethane (Table 1, entries 6 and 7).

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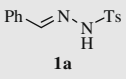
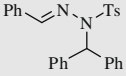
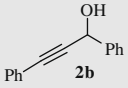
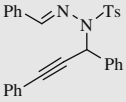
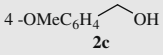
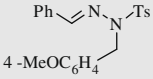
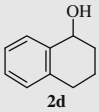
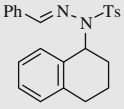
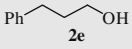
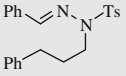
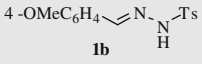
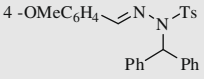
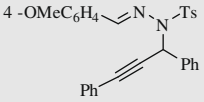
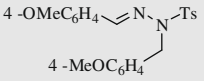
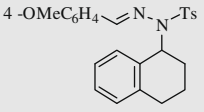
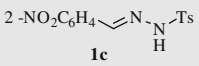
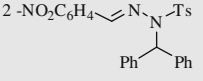
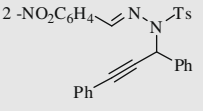
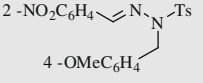
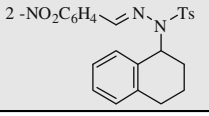
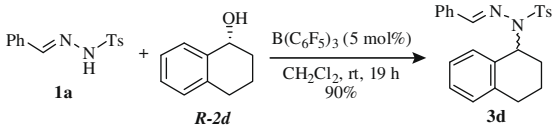
Under the optimized conditions, we next investigated the reaction of aldehyde tosylhydrazones with benzylic alcohols under the present conditions. The results are summarized in Table 2. N-Alkylation of *N*′-benzylidene-4-methylbenzenesulfonohydrazide (**1a**) with benzylic

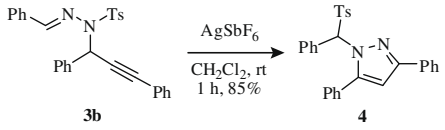
Table 2
$B(C_6F_5)_3$-catalyzed N-alkylation of aldehye tosylhydrazones using benzylic alcohols

Entry	Tosyl hydrazone	Benzylic alcohol	Reaction time (h)	Product[a]	Yield[b] (%)
1	 **1a**	 **2a**	20	 **3a**	90
2	**1a**	 **2b**	19	 **3b**	92
3	**1a**	 **2c**	22	 **3c**	89
4	**1a**	 **2d**	19	 **3d**	91
5	**1a**	 **2e**	24	 **3e**	0[c]
6	 **1b**	**2a**	21	 **3f**	89
7	**1b**	**2b**	19	 **3g**	89
8	**1b**	**2c**	22	 **3h**	87
9	**1b**	**2d**	19	 **3i**	90
10	 **1c**	**2a**	19	 **3j**	91
11	**1c**	**2b**	18	 **3k**	92
12	**1c**	**2c**	20	 **3l**	87
13	**1c**	**2d**	19	 **3m**	91

[a] All the products were characterized by ^1H, ^{13}C NMR and mass spectra.
[b] Isolated yields.
[c] No reaction either at room temperature or at 40 °C.



Scheme 2. *N*-alkylation with enantiopure alcohol ***R*-2d**.



Scheme 3. Synthesis of pyrazole **4** from **3b**.

alcohols **2b** to **2d** in the presence of $B(C_6F_5)_3$ in dichloromethane gave the corresponding *N*-alkylated products **3b** to **3d,** respectively, in good yields (Table 2, entries 2–4). However, the reaction of **1a** with 3-phenyl-1-propanol (**2e**) did not proceed under the present reaction conditions (Table 2, entry 5). This may be due to the non-benzylic nature of the alcohol. However, the reaction of *N*′-(4-methoxybenzylidene)-4-methylbenzenesulfonohydrazide (**1b**) and 4-methyl-*N*′-(-2-nitrobenzylidene) benzenesulfonohydrazide (**1c**) with benzylic alcohols **2a** to **2d** proceeded smoothly to give the corresponding N-alkylated products **3f** to **3m** in good yields (Table 2, entries 6–13).

To check the configuration of enantiopure secondary benzylic alcohols during the N-alkylation, the reaction of **1a** with enantiopure **2d** (***R*-2d**) was carried out under the present reaction conditions, which gave the corresponding N-alkylated product **3d** with loss of configuration.[8] This may be due to the initial formation of carbocation from benzylic alcohol followed by the reaction with hydrazone (Scheme 2).

Furthermore, we have demonstrated the utility of the N-alkylated hydrazone products in the synthesis of pyrazole products. The reaction of N-alkylated tosylhydrazone **3b** with silver hexafluoroantimonate in dichloromethane at room temperature gave the 3,5-diphenyl-1-(phenyl(tosyl) methyl)-1*H*-pyrazole **4** in 85% yield (Scheme 3).[6e]

In conclusion, we have developed an acid-catalyzed N-benzylation of tosylhydrazones using benzylic alcohols as alkylating agents for the first time. The reaction conditions were mild and efficient and provided the products in excellent yields. The applicability of N-alkylated hydrazones has also been successfully demonstrated for the synthesis of pyrazole.

General experimental procedure for $B(C_6F_5)_3$-catalyzed N-alkylation of aldehyde tosylhydrazones using benzylic alcohols: To a stirred solution of benzylic alcohol **2** (1 mmol) in dichloromethane (5 mL) were added tosyl hydrazone **1** (1 mmol) and 5 mol % $B(C_6F_5)_3$. The reaction mixture was stirred at room temperature and the reaction progress was monitored by TLC analysis. After the completion of the reaction (for reaction time, see Table 2), the mixture was evaporated in vacuo. The residue was purified by column chromatography on silica gel using ethyl acetate and hexanes as eluent to give the corresponding N-alkylated products.[9]

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8. *The enantioselectivity was checked using chiral HPLC*: chiral pak IA 250 × 4.6 mm, 5 μ, mobile phase: 5% *iso*-propanol in hexanes, flow rate: 1 mL/min., retention time: 15.50 (47.4%), 23.15 (52.5%).
9. *Spectral data of representative new products* (**3a**): White solid; mp 149–153 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.16 (s, 1H), 7.48–7.38 (m, 3H), 7.29–7.19 (m, 14H), 7.07 (d, 2H, J = 8.1 Hz), 6.85 (s, 1H), 2.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 151.7, 143.7, 138.2, 135.4, 134.4, 130.2, 128.5, 128.5, 128.5, 128.5, 128.5, 128.5, 128.1, 128.1, 128.1, 128.1, 128.1, 128.1, 128.1, 127.4, 127.4, 127.4, 127.4, 127.4, 67.0, 21.5; IR (KBr): ν 3747, 3436, 3025, 1599, 1344, 1132, 697 cm^{-1}; HRMS-ESI calcd for $C_{27}H_{24}N_2O_2SNa$: 463.1456; found: 463.1435.
Compound (**3b**): Brown solid; mp 125–129 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.98 (d, 2H, J = 8.3 Hz), 7.82 (s, 1H), 7.75 (d, 2H, J = 8.1 Hz), 7.56–7.53 (m, 2H), 7.45 (t, 2H, J = 7.5 Hz), 7.38–7.23 (m, 9H), 7.12 (d, 2H, J = 8.1 Hz), 6.92 (s, 1H), 2.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.2, 144.3, 136.1, 134.8, 134.3, 131.7, 130.2, 129.9, 129.9, 129.5, 129.5, 129.1, 129.15, 128.9, 128.9, 128.8, 128.8, 128.7, 128.4, 128.3, 128.3, 127.6, 126.9, 126.9, 122.1, 89.4, 81.8, 54.5, 21.6; IR (KBr): ν 3423, 3024, 2917, 1967, 1598, 1359 cm^{-1}; HRMS-ESI calcd for $C_{29}H_{24}N_2O_2SNa$: 487.1456; found: 487.1450.
Compound (**3c**): Light brown solid; mp 121–125 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.89 (d, 2H, J = 9.0 Hz), 7.52 (s, 1H), 7.38–7.23 (m, 8H), 7.11–7.03 (m, 3H), 5.86 (dd, 1H, J = 6.7, 4.5 Hz), 2.76 (m, 2H), 2.44 (s, 3H), 2.01 (m, 2H), 1.77 (m, 2H); ^{13}CNMR (75 MHz, $CDCl_3$): δ 148.1, 144.0, 137.1, 136.4, 134.4, 134.3, 129.9, 129.7, 129.3, 129.3, 128.5, 128.5, 128.3, 128.3, 127.5, 127.2, 127.2, 127.2,126.8, 58.4, 29.4, 24.7, 22.4, 21.7; IR (KBr): ν 3434, 3063, 2947, 1911, 1601, 1397, 1162, 996, 695 cm^{-1}; HRMS-ESI calcd for $C_{24}H_{24}N_2O_2SNa$: 427.1456; found: 427.1435.
Compound (**3d**): Off-white solid; mp:130–133.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.84 (d, 2H, J = 8.3 Hz), 7.65 (s, 1H), 7.53–7.48 (m, 1H), 7.34–7.20 (m, 8H), 6.83 (d, 2H, J = 8.3 Hz), 4.73 (s, 2H), 3.78 (s, 3H), 2.44 (s, 3H) ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.3, 147.4, 144.2, 134.8, 134.2, 130.3, 129.7, 129.7, 128.7, 128.7, 128.5, 128.5, 128.5, 127.6, 127.6, 127.5, 127.5, 114.5, 114.5, 55.4, 51.9, 21.7; IR (KBr): ν 3737, 3023, 2917, 1606, 1407, 1171, 904, 661; HRMS-ESI calcd for $C_{22}H_{22}N_2O_3SNa$: 417.1248; found: 417.1229.
Compound (**4**): Off-white solid; mp 172–175 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.82–7.74 (t, 4H, J = 6.9 Hz), 7.49–7.23 (m, 13H), 7.12 (d, 2H, J = 8.1 Hz), 6.61 (s, 1H), 6.25 (s, 1H), 2.44 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 152.1, 147.8, 144.9, 133.1, 130.7, 130.7, 130.2, 129.8, 129.8, 129.2, 129.2, 129.2, 129.2, 128.9, 128.7, 128.7, 128.7, 128.5, 128.5, 128.4, 128.4, 128.1, 126.9, 125.7, 125.7, 103.8, 80.8, 21.6; IR (KBr): ν 3060, 2937, 1897, 1591, 1449, 1077, 814, 697 cm^{-1}; HRMS-ESI calcd for $C_{29}H_{24}N_2O_2SNa$: 487.1456; found: 487.1469.