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ORIGINAL PAPER

Iodine-catalyzed N-alkylation of tosylhydrazones with benzylic alcohols

P. Theerthagiri · A. Lalitha

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Abstract A new and highly efficient method for the C–N bond formation using molecular iodine-catalyzed N-alkylation reaction of tosylhydrazones with benzylic/benzhydryl alcohols at room temperature in methylene chloride is described. A variety of tosylhydrazones reacted readily with various substituted benzylic alcohols in presence of 20 mol % iodine under mild reaction conditions to produce the corresponding biologically active N-alkylated compounds in good to excellent yields.

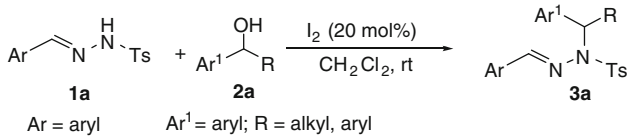
Keywords N-alkylation · Molecular iodine · Tosylhydrazones · Benzylic alcohols

Introduction

The N-alkylation of tosylhydrazones represents one of the most important C–N bond formation methodologies in organic synthesis [1]. The N-alkylated hydrazones have various applications in organic synthesis as useful synthons [2–6] and hydrazones constitute an important class of biologically active drug molecules [7] which have attracted attention of medicinal chemists due to their wide range of pharmacological properties. These compounds are being synthesized as drugs by many researchers to combat diseases with minimal toxicity and maximal effects. A number of hydrazone derivatives have been reported to exert notably antimicrobial, antihypertensive, anticonvulsant, analgesic, anti-inflammatory, antituberculosis, antitumoral, antiproliferative and antimalarial activities [8]. Biological activities of various hydrazones are well reported in the literature. Generally, this transformation is carried out using alkyl halides in the presence of stoichiometric amount of base [9, 10]. But, the use of alkyl halides is undesirable from an environmental point of view, and it generates wasteful salts as by-products. Cahhi et al. [11] reported the N-alkylation of tosylhydrazones using phase transfer catalyst. Among a variety of approaches for the N-alkylation of tosylhydrazones, alcohols are arguably one of the most ideal substrates that are receiving more attention [12, 13]. In principle, C–N bond formation by direct substitution of a hydroxyl group is difficult because of its poor leaving group ability. Therefore, hydroxyl groups usually require pre-activation through transformation into good leaving groups such as halides, carboxylates, and carbonates before treatment with tosylhydrazones. However, such a process inevitably produces salt waste, which would set limits for the industrial application and for the scope of substrates. Recently, DEAD/Ph_3P (Mitsunobu reaction), as well as acid catalyst systems such as $B(C_6F_5)_3$ have been proved to be successful for the N-alkylation of tosylhydrazones using alcohols as electrophiles directly [1, 14, 15]. Despite significant recent advances in this area, there remains room for improvement, such as increase in catalyst stability, lowering reaction temperature and increase in yield in the carbon–nitrogen single bond formation between tosylhydrazones with an alcohol.

To the best of our knowledge, there is only one report on the N-alkylation of tosylhydrazones with alcohols in the presence of acid catalyst [1], and there are no examples of the iodine-catalyzed N-alkylation of tosylhydrazones with alcohols. Therefore, development of a general, efficient and readily available catalyst like molecular

P. Theerthagiri · A. Lalitha (✉)
Department of Chemistry, Periyar University, Salem 636 011, Tamil Nadu, India
e-mail: lalitha2531@yahoo.co.in



Scheme 1 Molecular iodine-catalyzed N-alkylation of tosylhydrazones

iodine for this valuable but challenging transformation is highly desirable.

In recent years, molecular iodine has received considerable attention as an inexpensive, non-toxic, readily available catalyst for various organic transformations due to its moderate Lewis acidity and water tolerance [16–22]. Molecular iodine has been used to be a versatile catalyst for alkylation of 1,3 dicarbonyl compounds and 4-hydroxycoumarines [23, 24], synthesis of bis(indolyl)methane [25], Michael addition of indole and pyrrole to nitroolefins [26], etc. More recently, iodine-catalyzed transformation of molecules containing oxygen functional groups has been reported in the literature [27]. As part of our ongoing program on organic transformations [28, 29], herein we describe a highly efficient method for the C–N bond formation via molecular iodine-catalyzed N-alkylation reaction of tosylhydrazones with benzylic as well as benzhydric alcohols (Scheme 1).

Experimental

General

Iodine was purchased from Spectra Chem. All other chemicals were procured from S.D. Fine. Chem. Limited and used as received. Reactions were monitored by thin layer chromatography (TLC). TLC was performed on Merck pre-coated aluminum sheets of 60 F-254 silica gel plates with visualization by UV-light using ethyl acetate and *n*-hexane as solvent system. Melting points were determined in capillary tubes using Bűchi Melting Point B-545 apparatus. The IR spectra (neat) were recorded on a Nicolet 6700 FT-IR spectrometry. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ with Bruker 400 MHz high-resolution NMR spectrometers. $CDCl_3$ was used as the solvent for the NMR spectral measurements and spectra were recorded in parts per million with TMS as internal standard. Multiplicities are abbreviated as follows: singlet (s), doublet (d), triplet (t), multiplet (m) and broad (br). The mass spectra were recorded on GC–MS-Agilent 5975 series. Column chromatography was performed on silica gel (230–400 mesh) supplied by Acme Chemical Co. (India) for compound purification.

General experimental procedure for iodine-catalyzed N-alkylation of aldehyde tosylhydrazones using benzylic alcohols

To a stirred solution of benzylic alcohol (1 mmol) in dichloromethane (5 ml), tosylhydrazone (1.2 mmol) and 20 mol % iodine were added. The reaction mixture was stirred at room temperature for appropriate time mentioned in Table 2 and the reaction was monitored by TLC. After the completion of the reaction, the mixture was quenched with 10 % solution of sodium thiosulfite and separated organic layer was washed with water, brine and then concentrated. The crude solid was washed with 10 % hexane in ethyl acetate to give the corresponding N-alkylated products.

Compounds **3d** and **3p** [1] were previously reported and their structures were confirmed by comparison of their spectroscopic data with the reported data. Characterization data for some new compounds are given below.

*Compound (**3a**)*

Pale yellow solid. m.p.: 125–128 °C. IR (neat): ν = 3,021, 2,938, 1,593, 1,167 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.13 (s, 1H, =CH–), 7.68–7.76 (dd, 2H, ArH), 7.59–7.57 (dd, J = 9.6 Hz, 2H, ArH), 7.35–7.40 (m, 5 H, ArH), 7.22–7.30 (m, 5H, ArH) 5.67–5.72 (q, J = 7.2 Hz, 1H, CH), 2.40 (s, 3H, Ar–CH_3), 1.48–1.49 (d, J = 6.8 Hz, 3H, –CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): 153.83, 143.86, 140.83, 135.77, 134.31, 130.49, 129.47, 128.65, 128.50, 128.12, 127.64, 127.40, 127.11, 58.70, 21.58, 16.92 ppm. LC–MS: *m/z* cacld for $C_{22}H_{22}N_2O_2S$ 378.14; found 379.2 (M^+).

*Compound (**3b**)*

Pale yellow oil. IR (neat): ν = 3,024, 2,945, 1,596, 1,339, 1,162 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11 (s, 1H, =CH–), 7.69–7.71 (dd, J = 8.4 Hz, 2H, ArH), 7.57–7.59 (dd, J = 9.2 Hz, 2H, ArH), 7.34–7.40 (m, 5 H, ArH), 7.21–7.28 (m, 2H, ArH), 7.03–7.14 (m, 2H, ArH) 5.64–5. (q, J = 6.8 Hz, 1H, CH), 2.41 (s, 3H, Ar–CH_3), 2.32 (s, 3H, Ar–CH_3), 1.45–1.47 (d, J = 7.2 Hz, 3H, –CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): 153.60, 143.77, 137.77, 137.05, 135.87, 134.36, 130.41, 129.42, 129.15, 128.61, 128.11, 127.61, 126.99, 58.44, 21.57, 21.03, 16.77 ppm. LC–MS: *m/z* cacld for $C_{23}H_{24}N_2O_2S$ 392.16; found 392.9 (M^+).

*Compound (**3c**)*

Light brown solid. m.p.: 110–113 °C. IR (neat): ν = 3,060, 2,919, 1,686, 1,588, 1,338, 1,162 cm^{-1}. ^{1}H NMR

(400 MHz, $CDCl_3$): δ = 8.25 (s, 1H, =CH–), 7.60–7.62(m, 4H, ArH), 7.37–7.42 (m, 3H, ArH), 7.30–7.32 (m, 2H, ArH), 7.21–7.27 (m, 4H, ArH), 5.54–5.59 (q, *J* = 7.2 Hz, 1H, CH), 2.41 (s, 3H, Ar–CH_3), 1.27 (d, 3H, *J* = 7.2 Hz, Ar–CH_3), 1.45–1.47 (d, *J* = 6.8 Hz, 3H, –CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): 1,156.15, 144.01, 139.38, 135.55, 134.06, 133.28, 130.83, 129.45, 128.73, 128.70, 128.49, 128.01, 127.82, 58.45, 21.56, 17.56 ppm. LC–MS: *m/z* cacld for $C_{22}H_{21}N_2O_2S$ 412.9; found 413.2 (M^+).

*Compound (**3e**)*

Pale yellow solid. m.p.: 118–121 °C. IR (neat): ν = 3,021, 2,940, 1,591, 1,339 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.14 (s, 1H, =CH–), 7.50–7.52 (dd, *J* = 8.4 Hz, 2H, ArH), 7.41–7.44 (m, 2H, ArH), 7.21–7.32 (m, 7H, ArH), 7.14–7.16 (dd, *J* = 8.0 Hz, 2H, ArH) 7.08–7.10 (dd, *J* = 8.0 Hz, 2H, ArH), 7.02–7.04 (dd, *J* = 8.0 Hz, 2H, ArH), 6.86 (s, 1H, CH), 2.35 (s, 3H, Ar–CH_3), 2.30 (s, 3H, Ar–CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): 151.38, 143.70, 138.40, 137.18, 135.50, 135.15, 134.47, 130.14, 129.15, 129.09, 129.04, 128.90, 128.55, 128.19, 127.43, 127.37, 66.74, 21.52, 21.06 ppm. LC–MS: *m/z* cacld for $C_{28}H_{26}N_2O_2S$ 454.0; found 455.2 (M^+).

*Compound (**3f**)*

Pale yellow oil. IR (neat): ν = 3,025, 2,939, 1,598, 1,337, 1,162 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.24 (s, 1H, =CH–), 7.44–7.51 (m, 5H, ArH), 7.31–7.36 (m, 4H, ArH), 7.17–7.25 (m, 6H, ArH), 7.05–7.12 (m, 4H, ArH), 2.36 (s, 3H, Ar–CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): 152.11, 143.89, 137.63, 136.52, 135.34, 133.98, 131.27, 130.37, 129.51, 129.20, 129.04, 128.84, 128.64, 128.29, 128.09, 127.56, 126.51, 64.44, 21.54 ppm. LC–MS: *m/z* cacld for $C_{27}H_{23}ClN_2O_2S$ 474.12; found 475.2 (M^+).

*Compound (**3g**)*

White solid. m.p.: 133–136 °C. IR (neat): ν = 3,059, 2,982, 1,597, 1,350, 1,166 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.26 (s, 1H, =CH–), 7.84–7.86 (dd, *J* = 9.2 Hz, 1H, ArH), 7.78–7.80 (dd, *J* = 8.0 Hz, 2H, ArH), 7.42–7.44 (d, *J* = 7.6 Hz, 2H, ArH), 7.22–7.35 (m, 8H, ArH), 5.92–5.94 (q, *J* = 7.2 Hz, 1H, CH), 2.40 (s, 3H, Ar–CH_3), 1.60–1.62 (d, *J* = 6.8 Hz, 3H, –CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): 144.12, 143.86, 140.08, 135.69, 134.28, 132.10, 129.65, 129.59, 128.72, 128.22, 127.51, 126.90, 126.78, 57.80, 21.60, 16.13 ppm. LC–MS: *m/z* cacld for $C_{22}H_{21}ClN_2O_2S$ 412.10; found 413.2 (M^+).

*Compound (**3h**)*

White solid. m.p.: 140–143 °C. IR (neat): ν = 3,061, 2,982, 1,596, 1,380, 1,165 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.25 (s, 1H, =CH–), 7.83–7.85 (dd, *J* = 9.6 Hz, 1H, ArH), 7.78–7.80 (d, *J* = 8.4 Hz, 2H, ArH), 7.21–7.31 (m, 7H, ArH), 7.12–7.14 (d, *J* = 8.0 Hz, 2H, ArH), 5.86–5.91(q, *J* = 7.2 Hz, 1H, CH), 2.41 (s, 3H, Ar–CH_3), 2.32 (s, 3H, Ar–CH_3), 1.55–1.59 (d, *J* = 12.8 Hz, 3H, –CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): 144.05, 143.74, 137.17, 136.99, 135.80, 134.26, 132.16, 130.61, 129.63, 129.56, 129.36, 128.35, 128.20, 126.88, 126.80, 126.71, 57.61, 21.60, 21.04, 16.03 ppm. LC–MS: *m/z* cacld for $C_{23}H_{23}ClN_2O_2S$ 426.10; found 427.2 (M^+).

*Compound (**3i**)*

Off white solid. m.p.: 121–123 °C. IR (neat): ν = 3,024, 2,945, 1,596, 1,339, 1,162 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.34 (s, 1H, =CH–), 7.82–7.84 (dd, *J* = 9.6 Hz, 1H, ArH), 7.73–7.75 (d, *J* = 8.4 Hz, 2H, ArH), 7.31–7.33 (m, 7H, ArH), 7.25–7.29 (m, 2H, ArH), 5.79–5.84 (q, *J* = 7.2 Hz, 1H, CH), 2.42 (s, 3H, Ar–CH_3), 1.55–1.57 (d, *J* = 8.8 Hz, 3H, –CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): 144.33, 144.31, 138.81, 135.48, 134.43, 133.41, 131.90, 130.94, 129.76, 129.63, 128.77, 128.34, 128.13, 126.96, 126.84, 57.55, 21.60, 16.69 ppm. LC–MS: *m/z* cacld for $C_{22}H_{20}Cl_2N_2O_2S$ 446.06; found 447.2 (M^+), 449.0 (M + 2).

*Compound (**3j**)*

Brown solid. m.p.: 137–139 °C. IR (neat): ν = 3,060, 2,941, 1,686, 1,588, 1,332, 1,161 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.39 (s, 1H, =CH–), 7.61–7.64 (m, 3H, ArH), 7.73–7.75 (d, *J* = 8.4 Hz, 2H, ArH), 7.21–7.32 (m, 9H, ArH), 7.15–7.19 (m, 5H, ArH), 7.11(s,1H, CH), 2.38 (s, 3H, Ar–CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): 144.16, 142.89, 137.89, 135.25, 134.20, 130.52, 130.08, 129.61, 129.37, 128.96, 128.40, 127.63, 127.44, 127.28, 126.85, 126.75, 66.46, 21.57 ppm. LC–MS: *m/z* cacld for $C_{27}H_{23}ClN_2O_2S$ 474.12; found 447.2 (M + 2), 475.2 (M^+).

*Compound (**3k**)*

Pale yellow solid. m.p.: 111–113 °C. IR (neat): ν = 3,032, 2,944, 1,682, 1,581, 1,336, 1,165 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.36 (s, 1H, =CH–), 7.63.–7.66 (m, 3H, ArH), 7.26–7.28 (m, 4H, ArH), 7.19–7.24 (m, 8H, ArH), 7.09–7.18 (m, 3H, ArH) 2.38 (s, 3H, Ar-CH_3), 2.33

(s, 3H, Ar–CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): 144.09, 142.73, 138.00, 137.35, 135.38, 134.75, 134.18, 132.19, 130.45, 129.59, 129.34, 129.07, 128.94, 128.85, 128.37, 127.52, 126.82, 126.76, 66.21, 21.57, 21.09 ppm. LC–MS: *m/z* cacld for $C_{28}H_{25}ClN_2O_2S$ 488.13; found 489.2 (M^+).

*Compound (**3l**)*

Pale yellow oil. IR (neat): ν = 3,026, 2,939, 1,598, 1,337, 1,162 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.37 (s, 1H, =CH–), 7.66.–7.68 (m, 3H, ArH), 7.27–7.29 (m, 4H, ArH), 7.22–7.25 (m, 8H, ArH), 7.09–7.20 (m, 3H, ArH) 2.38 (s, 3H, Ar–CH_3), 2.33 (s, 3H, Ar–CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): 144.11, 142.83, 138.03, 137.35, 135.58, 134.85, 134.20, 132.21, 130.46, 129.55, 129.35, 129.08, 128.95, 128.86, 128.39, 127.55, 126.89, 126.78, 66.23, 21.59, 21.09 ppm. LC–MS: *m/z* cacld for $C_{27}H_{22}Cl_2N_2O_2S$ 508.13; found 509.2 (M^+).

*Compound (**3n**)*

Brown oil. IR (neat): ν = 3,025, 2,937, 1,596, 1,333, 1,169 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.08 (s, 1H, =CH–), 7.67.–7.71 (m, 2H, ArH), 7.35–7.38 (m, 2H, ArH), 7.18–7.29 (m, 5H, ArH), 7.08–7.14 (m, 2H, ArH),6.90–6.93 (m, 1H, ArH), 5.68–5.70 (q, *J* = 7.2 Hz, 1H, CH), 5.29 (s, 3H, –CH_3), 3.81 (s, 3H, Ar–OCH_3), 2.39 (s, 3H, Ar–CH_3) 1.47–149(s, *J* = 7.2 Hz, 3H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): 159.79, 152.79, 143.94, 140.75, 135.73, 129.66, 129.48, 129.31, 128.61, 128.53, 128.43, 128.14, 127.68, 127.57, 127.43, 127.07, 120.63, 116.71, 116.58, 116.45, 111.93, 58.62, 55.30, 53.47, 21.58, 16.89 ppm. LC–MS: *m/z* cacld for $C_{23}H_{24}N_2O_3S$ 408.51; found 409.2 (M^+).

*Compound (**3o**)*

Pale yellow oil. IR (neat): ν = 3,032, 2,939, 1,598, 1,337, 1,162 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.18(s, 1H, =CH–), 7.67.–7.71 (m, 2H, ArH), 7.60–7.62 (d, *J* = 8.4 Hz, 1H, ArH), 7.25–7.31 (m, 3H, ArH), 7.13–7.22 (m, 7H, ArH), 6.94–6.96 (m, 1H, ArH), 5.56–5.58 (q, *J* = 7.2 Hz, 1H, CH), 3.83 (s, 3H, Ar–OCH_3), 2.40 (s, 3H, Ar–CH_3) 1.43–145 (s, *J* = 6.8 Hz, 3H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): 159.83, 155.14, 144.07, 139.34, 135.55, 135.47, 133.29, 129.75, 129.47, 128.82, 128.67, 128.52, 128.02, 120.78, 116.69, 112.22, 58.39, 55.33, 21.57, 17.52 ppm. LC–MS: *m/z* cacld for $C_{23}H_{23}ClN_2O_3S$ 442.9; found 443.2 (M^+).

*Compound (**3r**)*

Yellow oil. IR (neat): ν = 3,032, 2,946, 1,594, 1,335, 1,160 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.38–8.40 (dd, *J* = 8.4 Hz 2H, ArH), 7.89 (s, 1H, =CH–), 7.76–7.78 (dd, *J* = 8.0 Hz, 2H, ArH), 7.60–7.62 (dd, *J* = 8.8 Hz, 2H, ArH), 7.25–7.31 (m, 4H, ArH), 7.11–7.17 (m, 2H, ArH), 5.87–5.93 (q, *J* = 7.2 Hz, 1H, CH), 2.43 (s, 3H, Ar–CH_3), 2.33 (s, 3H, Ar–CH_3), 1.59–1.61 (d, *J* = 7.2 Hz, 3H, –CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): 148.15, 144.50, 143.16, 140.63, 137.45, 136.71, 135.60, 130.49, 129.49, 128.02, 127.46, 126.56, 125.35, 124.31, 123.90, 58.03, 21.62, 21.04, 16.59 ppm. LC–MS: *m/z* cacld for $C_{23}H_{23}N_3O_4S$ 437.51; found 438.2 (M^+).

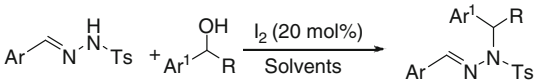
*Compound (**3s**)*

Yellow oil. IR (neat): ν = 3,026, 2,939, 1,597, 1,336, 1,160 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.18–8.21 (dd, *J* = 8.8 Hz, 2H, ArH), 8.03 (s, 1H, =CH–), 7.66–7.72 (dd, *J* = 8.4 Hz, 2H, ArH), 7.64–7.66 (dd, *J* = 8.0 Hz, 2H, ArH), 7.26–7.33 (m, 7H, ArH), 5.81–5.83 (q, *J* = 7.2 Hz, 1H, CH), 2.43 (s, 3H, Ar–CH_3), 1.58–1.60 (d, *J* = 7.2 Hz, 3H, –CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): 148.37, 144.92, 144.76, 140.32, 138.59, 135.33, 133.64, 129.83, 128.89, 128.60, 127.91, 127.62, 126.80, 123.98, 69.75, 58.03, 25.30, 21.62, 17.26 ppm. LC–MS: *m/z* cacld for $C_{22}H_{20}$ ClN_3O_4S 457.9; found 458.0 (M^+), 459.2 (M + 2).

*Compound (**3t**)*

Yellow oil. IR (neat): ν = 3,032, 2,938, 1,597, 1,334, 1,164 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.12–8.36

Table 1 Optimizing the reaction conditions for the N-alkylation of tosylhydrazone (**1a**) with 1-phenylethanol **(2a)** using iodine as catalyst

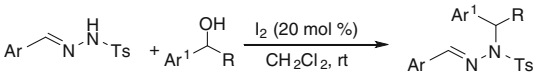


Entry	Solvent	*T* (°C)	Time (h)	Yield (%)[a]
1	DMSO	25	25	–
2	THF	25	25	10
3	$C_2H_4Cl_2$	25	20	80
4	CH_3CN	25	20	55
5	CH_2Cl_2	25	20	92
6	CH_3NO_2	25	25	60

All reactions were performed with tosylhydrazone (1a; 1 mmol), 1-phenylethanol (**2a**; 1.2 mmol), and iodine (20 mol %) in the indicated solvent

[a] Isolated yield after washing with 10 % hexane in ethyl acetate

Table 2 Iodine-catalyzed N-alkylations of aldehyde tosylhydrazones using benzylic alcohols



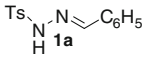
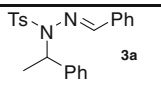
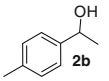
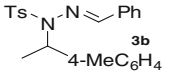
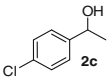
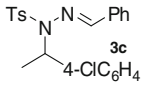
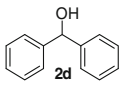
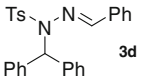
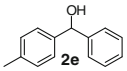
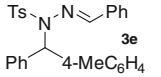
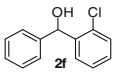
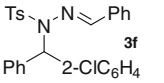
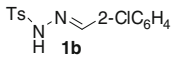
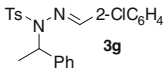
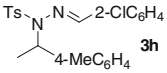
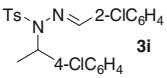
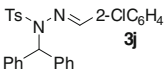
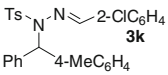
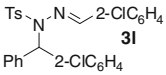
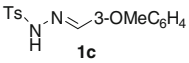
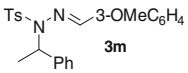
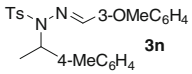
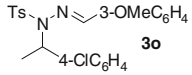
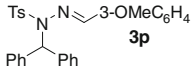
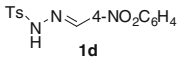
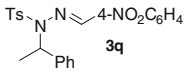
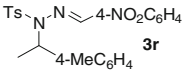
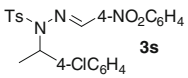
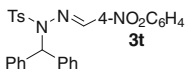
Entry	Tosylhydrazone	Benzylic alcohol	Time (h)	Product	Yield (%)[a]
1	 **1a**	 **2a**	18	 **3a**	92
2	**1a**	 **2b**	18	 **3b**	88
3	**1a**	 **2c**	20	 **3c**	80
4	**1a**	 **2d**	18	 **3d**	83
5	**1a**	 **2e**	20	 **3e**	78
6	**1a**	 **2f**	20	 **3f**	90
7	 **1b**	**2a**	20	 **3g**	92
8	**1b**	**2b**	18	 **3h**	81
9	**1b**	**2c**	18	 **3i**	86
10	**1b**	**2d**	18	 **3j**	80
11	**1b**	**2e**	20	 **3k**	65
12	**1b**	**2f**	18	 **3l**	52
13	 **1c**	**2a**	18	 **3m**	75

Table 2 continued

Entry	Tosylhydrazone	Benzylic alcohol	Time (h)	Product	Yield (%)[a]
14	**1c**	**2b**	20	 **3n**	66
15	**1c**	**2c**	18	 **3o**	55
16	**1c**	**2d**	20	 **3p**	63
17	 **1d**	**2a**	20	 **3q**	95
18	**1d**	**2b**	18	 **3r**	90
19	**1d**	**2c**	18	 **3s**	83
20	**1d**	**2d**	20	 **3t**	78

All reactions were performed with tosylhyrdrazones (1 mmol), benzylic alcohols (1.2 mmol), and iodine (20 mol %) in dichloromethane

[a] Isolated yield after washing with 10 % hexane in ethyl acetate

(dd, $J = 8.4$ Hz 2H, ArH), 8.0 (s, 1H, =CH–), 7.62–7.68 (dd, $J = 8.0$ Hz, 2H, ArH), 7.45–7.49 (dd, $J = 8.4$ Hz, 2H, ArH), 7.22–7.40 (m, 10H, ArH), 7.14–7.20 (m, 2H, ArH), 7.10 (s, 1H, CH), 2.38 (s, 3H, Ar–CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): 148.08, 144.63, 142.39, 142.23, 140.64, 137.69, 135.11, 133.19, 130.00, 129.60, 129.28, 129.06, 128.84, 128.68, 128.39, 127.86, 127.44, 127.39, 127.28, 127.07, 126.56, 126.45, 123.90, 80.03, 66.83, 21.61 ppm. LC–MS: *m/z* cacld for $C_{27}H_{23}N_3O_4S$ 485.14; found 486.2 (M^+).

Results and discussion

Initially, we attempted the N-alkylation of N-benzylidene-4-methylbenzene sulfonohydrazide (**1a**) with 1-phenylethanol (**2a**) in dichloromethane using 20 mol % of iodine as catalyst and it was observed that the reaction went to completion at room temperature within 20 h to give product (**3a**) in 93 % yield (Scheme 1).

To obtain the optimized reaction conditions, we have chosen the reaction of *N*-benzylidene-4-methyl benzene sulfonohyrazide with 1-phenylethanol in presence of molecular iodine as Lewis acid catalyst. First we examined the solvent suitability for this reaction and the results are summarized in Table 1. The reaction in DMSO did not proceed well and in THF afforded only 10 % of the product with several unwanted side products. After substantial experimentation with different solvents ($C_2H_4Cl_2$ 80 % yield, CH_3CN 55 % yield, CH_3NO_2 60 % yield), dichloromethane (92 % yield) came out as a solvent of choice. With this encouraging result, next we investigated the amount of iodine required to catalyze the transformation. To start with, we have used 10 mol % of iodine which afforded the products in 45 % yield after 20 h. Use of 15 mol % of iodine improved the yield to 75 % with the reaction time almost same as that of 10 mol %. On the other hand, using 20 mol % of iodine as catalyst, the product yield was increased to 94 % in 20 h and 20 mol % of iodine has been used as catalyst for further reactions.

To check the versatility of iodine-catalyzed N-alkylation reaction, we next investigated the reaction of tosylhydrazones of different aldehydes with a series of substituted

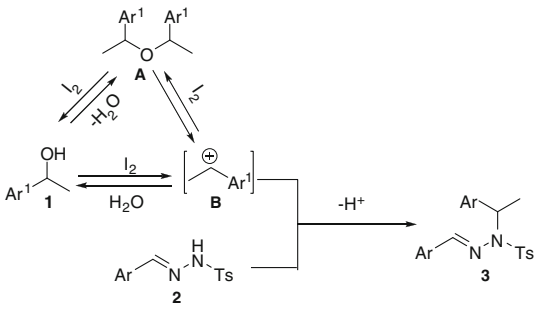


Fig. 1 Plausible mechanism for the iodine-catalyzed N-alkylation

benzylic alcohols under the optimized conditions. The results are summarized in Table 2.

N-alkylations of *N*′-benzylidene-4-methylbenzenesulfonohydrazide (**1a**) with benzylic alcohols (**2a**–**2f**) bearing electron-donating and electron-withdrawing groups on benzylic alcohols **2a**–**2f**, proceeded smoothly to give the corresponding N-alkylated products in moderate to good yields (entries 7–12, Table 2). Similarly, *N*′-(4-methylbenzylidence)-4-methylbenzene sulfonohydrazide (**1c**) and 4-methyl-*N*′-(-4-nitrobenzlidene)benzenesulfonohydrazide (**1d**) with benzylic alcohols **2a**–**2d** also undergo N-alkylation with smooth conversion to give the desired products in substantial yields (entries 13–16, Table 2). Next, the reaction was extended to simple primary alcohols such as benzyl alcohols as the substrates for N-alkylation of tosylhydrazones under the same reaction conditions, where, disappointingly, the corresponding N-alkylated products were obtained in low yields (10–15 %).

Although the exact mechanism is not known at this stage, it can only be speculated based on the experimental observations. We have previously observed that with a catalytic amount of iodine, benzylic alcohols were rapidly converted to dimeric either (**A**) by the elimination of water [28]. Presumably, in the presence of a nucleophile, the ether is polarized by iodine and generates more stable benzylic carbocation (**B**). The formation of benzylic carbocation is well documented and has been reported in the literature [30]. The nucleophilic attack of tosylhydrazone moiety on to the resulting benzylic carbocation generated the desired product (Fig. 1). Support for this mechanism was obtained from the isolation of the symmetric ether at the initial stages (within 1–2 h) whose structure was confirmed by NMR and which after appropriate time (mentioned in Table 1) was fully converted to the corresponding N-alkylated products. This concluded that iodine acts as mild Lewis acid and more efficient for this reaction. When the reaction was carried out in the presence of 20 mol % of iodine at room temperature for 4–6 h, it has been observed that the ether **A** was the major product and only with the increase in the mol % of iodine, the desired product was formed. Further, it was observed that the ether was completely converted to the desired product when the reaction was stirred at room temperature for 18–20 h.

Conclusions

In summary, we have successfully employed molecular iodine as an efficient catalyst to promote N-alkylation of tosylhydrazones using secondary benzylic alcohols, affording the N-alkylated tosylhydrazone derivatives in good to excellent yields. The notable advantages of this method are broad scope, mild reaction conditions, operational simplicity, direct use of alcohols and the use of inexpensive and non-toxic catalyst. This method is energy saving, environmentally friendly, since water is the only side product. In addition, due to the easy availability of the starting materials and catalyst, this reaction may prove to be very useful in organic synthesis. Further studies in this area to explore the mechanism and synthetic applications of this reaction are being carried out in our laboratory.

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References

1. C.R. Reddy, E. Jithender, Tetrahedron Lett. **50**, 5633 (2009)
2. S. Kobayashi, R. Hirabayashi, J. Am. Chem. Soc. **121**, 6942 (1999)
3. M. Movassaghi, O.K. Ahmed, Angew. Chem. Int. Ed. **47**, 8909 (2008)
4. J.G. Schantl, P. Hebeisen, P. Karpellus, Synth. Commun. **19**, 39 (1989)
5. Y.T. Lee, Y.K. Chung, J. Org. Chem. **73**, 4698 (2008)
6. D.A. Mundal, K.E. Lutz, R. Thomson, R. J. Org. Lett. **11**, 465 (2009)
7. H.S. Seleem, G.A. El-Inany, B.A. El-Shetary, M.A. Mousa, Chem. Cent. J. **5**, 2 (2011)
8. S. Rollas, S.G. Kuçukguzel, Molecules **12**, 1910 (2007)
9. D.J. Benstead, A.N. Hulme, H. Mcnab, P. Wight, P. Synlett 1571 (2005)
10. R. He, Y. Lam, Org. Biomol. Chem. **6**, 62182 (2008)
11. S. Cahhi, F.L. Torre, D. Mistiti, Synthesis 301 (1977)
12. D.J. Brondani, D.R.M. De Moreira, M.P. De Farias, F.R. Da, S. Souza, F.F. Barbosa, A.C.L. Leite, Tetrahedron Lett. **48**, 3919 (2007)
13. K. Fujita, Z. Li, N. Ozeki, R. Yamaguchi, Tetrahedron Lett. **44**, 2687 (2003)
14. J.R. Henry, L.R. Marcin, M.C. Mcintosh, P.M. Scok, G.D. Harris, S.M. Weinreb, Tetrahedron Lett. **30**, 5709 (1989)
15. J.M. Keith, L.J. Gomez, J. Org. Chem. **71**, 7113 (2006)
16. K. Zmitek, M. Zupan, S. Stavber, J. Iskra, J. Org. Chem. **72**, 6534 (2007)
17. Y.M. Ren, C. Cai, Org. Prep. Proced. Int. **40**, 101 (2008)
18. R. Varala, S. Nuvula, S.R. Adapa, J. Org. Chem. **71**, 8283 (2006)
19. K. Zmitek, M. Zupan, S. Stavber, J. Iskra, Org. Lett. **8**, 2491 (2006)
20. J.S. Yadav, M. Satyanarayana, S. Raghavendra, E. Balanarsaiah, Tetrahedron Lett. **46**, 8745 (2005)

21. H. Veisi, Curr. Org. Chem. **15**, 2438 (2011)
22. A.K. Banerjee, W. Vera, H. Mora, M.S. Laya, L. Bedoya, E.V. Cabrera, J. Sci. Ind. Res. **65**, 299 (2006)
23. W. Rao, A.H.L. Tay, P.J. Goh, J.M.L. Choy, J.K. Ke, P.W.H. Chan, Tetrahedron Lett. **49**, 122 (2008)
24. X. Lin, X. Dai, Z. Mao, Y. Wang, Tetrahedron **65**, 9233 (2009)
25. S.J. Ji, Y.S. Wang, Y. Zhang, T.P. Loh, Tetrahedron **60**, 2051 (2004)
26. C. Lin, J. Hsu, M.N.V. Sastry, H. Fang, Z. Tu, J.T. Liu, Y.C. Fa, Tetrahedron **61**, 11751 (2005)
27. M. Jereb, D. Vrazic, M. Zupan, Tetrahedron **67**, 1355 (2011)
28. P. Theerthagiri, A. Lalitha, P.N. Arunachalam, Tetrahedron Lett. **51**, 2813 (2010)
29. P. Theerthagiri, A. Lalitha, Tetrahedron Lett. **51**, 5454 (2010)
30. M. Noji, Y. Konno, K. Ishii, J. Org. Chem. **72**, 5161 (2007)