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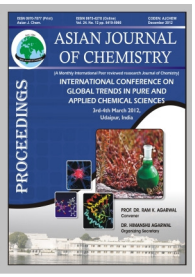

Direct Sulfamidation of Alcohols Using Magnetically Recoverable Pd/Fe_3O_4 as the Catalyst†

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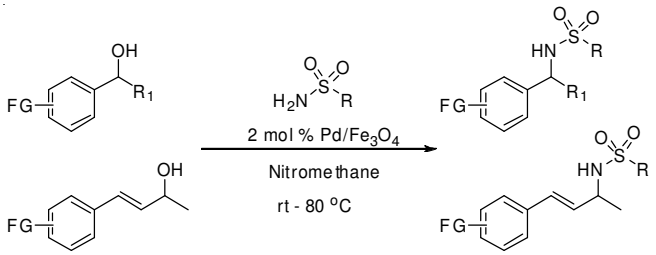
An efficient method is described for the direct amination of alcohols with sulfonamides using magnetically separable Pd/Fe_3O_4 as a catalyst without using any additives. Various alcohols such as benzylic alcohol and allylic alcohol underwent sulfamidation with sulfonamides gave the corresponding products in good to excellent yields. This effective catalyst requires no preactivation of the hydroxy group of alcohols and the reaction is environmentally benign with water as a by-product. The catalyst is completely recoverable with the simple application of an external magnetic field and the efficiency of the catalyst remains unaltered even after five cycles.

Key Words: Sulfamidation, Magnetically separable Pd/Fe_3O_4, Benzylic alcohols, Allylic alcohols, Sulfonamides.

INTRODUCTION

The development of versatile and efficient methods for the synthesis of amines has still been an active area of research[1], because a variety of amines is of significant importance for the bulk- and fine-chemical industries not only as building blocks for polymers and dyes, but also for the synthesis of new pharmaceuticals and agrochemicals[2]. Furthermore, a plethora of naturally bioactive compounds such as alkaloids, amino acids and nucleotides contain amino groups. The well-established transition-metal-catalyzed allylic aminations of allylic acetates and their derivatives have intrinsic drawbacks in terms of atom economy[3]. In the last decade, various catalytic aminations, such as palladium- and copper catalyzed amination of aryl halides[4-6], hydroamination[7-12] and hydroaminomethylation[13-16] of olefins or alkynes, have received increased attention. However, less interest has been paid to the further development of catalytic alkylations of amines, such a reductive amination[17,18].

Readily available benzylic alcohol and allylic alcohol are desirable substrates for the synthesis of benzylic amine and allylic amine. Substitution of the hydroxy group in alcohols by amine nucleophiles generally requires preactivation of the alcohols because of the poor leaving ability of the hydroxy group. Alcohols are generally transformed into the corresponding halides, carboxylates, carbonates, phosphonates or related compounds with good leaving groups. The process inevitably produces a stoichiometric amount of salt waste. The substitution of the halides and related compounds also produces salt waste and requires a stoichiometric amount of a base. Therefore, the direct catalytic substitution of alcohols with amines is desirable. As no stoichiometric hydroxy-group activator is utilized, the products are produced with water as the only waste. Herein, we described an efficient method for the direct amination of alcohols with sulfonamides using magnetically separable Pd/Fe_3O_4 as a catalyst without using any additives **(Scheme-I)**.



Scheme-I

EXPERIMENTAL

Experimental procedure: A mixture of benzyl alcohol (1 mmol), sulfonamide (1.2 mmol) and Pd/Fe_3O_4 (2 mol %) in nitromethane (5 mL) was stirred at temperature specified in Table- 3. After completion of the reaction as indicated by TLC, the reaction mixture was diluted with water and extracted with ethyl acetate (2 × 10 mL). The combined organic layers were

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dried over anhydrous Na_2SO_4, concentrated *in vacuo* and purified by column chromatography on silica gel to afford the pure product.

Spectroscopic data for the selected products

4-Methyl-*N*-(1-phenylethyl) benzenesulfonamide (Table-2, entry 1): IR (KBr, ν_{max}, cm^{-1}): 3252, 2971, 2587, 2274, 1593, 1496, 1429, 1327, 1158, 1081, 1014, 810. ^1H NMR (300 MHz, $CDCl_3$) δ 1.42 (d, 3H, *J* = 6.9 Hz), 2.39 (s, 3H), 4.47 (q, 1H, *J* = 6.9 Hz), 5.23 (d, 1H, *J* = 7.1 Hz), 7.10-7.13 (m, 2H), 7.16-7.19 (m, 5H), 7.63 (d, 2H, *J* = 8.1 Hz)). ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.4, 23.5, 53.6, 126.1, 127, 127.3, 128.4, 129.4, 137.6, 142, 143. ESI-MS (*m/z*): 289 $(M+Na)^+$.

***N*-Benzyl-4-methyl-benzenesulfonamide (Table-2, entry 3):** IR (KBr, ν_{max}, cm^{-1}): 3280, 2923, 1597, 1432, 1325, 1157, 1092, 860. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.41 (s, 3H), 4.04 (d, 2H, *J* = 6.3), 5.03 (t, 1H, *J* = 6.3 Hz), 7.02 (d, 2H, *J* = 8.3 Hz), 7.23-7.36 (m, 5H), 7.68 (d, 2H, *J* = 8.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 20.9, 47.0, 125.4, 127.1, 127.5, 128.3, 129.2, 133.2, 139.5, 143.4. ESI-MS (m/z): 262 (M+H).

(E)-4-methyl-*N*-(4-phenylbut-3-en-2-yl)benzenesulfonamide (Table 2, entry 6): IR (neat): 3290, 2973, 1594, 1422, 1328, 1152, 1085, 970. ^1H NMR (300 MHz, $CDCl_3$): δ 1.29 (d, 3H, *J* = 6.8 Hz), 2.36 (s, 3H), 4.00-4.13 (m, 1H), 4.67 (d, 1H, *J* = 7.5 Hz), 5.81 (dd, 1H, *J* = 6.8 Hz, 15.8 Hz), 6.27 (d, 1H, *J* = 15.8 Hz), 7.09-7.24 (m, 7H), 7.73 (d, 2H, *J* = 8.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.5, 22.1, 52.0, 120.4, 125.5, 126.8, 127.1, 127.4, 128.8, 129.5, 130.5, 142.9, 156.6. ESI MS (*m/z*): 324 (M + Na).

(E)-*N*-(4-(4-methoxyphenyl)but-3-en-2-yl)-4-methylbenzenesulfonamide (Table-2, entry 8): IR (neat, cm^{-1}): 3277, 2927, 1607, 1511, 1456, 1323, 1248, 1157, 1091, 1033, 968. ^1H NMR (300 MHz, $CDCl_3$): δ 1.27 (d, 3H, *J* = 6.8 Hz), 2.37 (s, 3H), 3.78 (s, 3H), 3.99-4.09 (m, 1H), 4.58 (d, 1H, *J* = 7.3 Hz), 5.66 (dd, 1H, *J* = 6.8 Hz, 15.8 Hz), 6.21 (d, 1H, *J* = 15.8 Hz), 6.74 (d, 2H, *J* = 8.6 Hz), 7.05 (d, 2H, *J* = 8.6 Hz), 7.20 (d, 2H, *J* = 7.9 Hz), 7.72 (d, 2H, *J* = 8.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.4, 21.9, 51.7, 55.2, 113.7, 127.2, 127.5, 127.9, 129.2, 129.5, 129.9, 138.0, 143.2, 159.2. ESI MS (*m/z*): 354 (M + Na).

(E)-*N*-(4-(benzo[d][1,3]dioxol-5-yl)but-3-en-2-yl)-4-methylbenzenesulfonamide (Table-2, entry 9): IR (neat, cm^{-1}): 3296, 2917, 1599, 1498, 1445, 1417, 1321, 1251, 1159, 1035, 964. ^1H NMR (300 MHz, $CDCl_3$): δ 1.26 (d, 3H, *J* = 6.6 Hz), 2.38 (s, 3H), 3.97 - 4.09 (m, 1H), 4.67 (d, 1H, *J* = 7.3 Hz), 5.62 (dd, 1H, *J* = 6.7 Hz, 15.8 Hz), 5.92 (s, 2H), 6.18 (d, 1H, *J* = 15.8 Hz), 6.54-6.60 (m, 2H), 6.66 (d, 1H, *J* = 7.9 Hz), 7.22 (d, 2H, *J* = 8.1 Hz), 7.72 (d, 2H, *J* = 8.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.4, 21.7, 51.6, 100.8, 105.6, 108.2, 121.1, 127.3, 128.4, 129.6, 130.1, 130.6, 138.0, 143.4, 147.2, 147.7. ESI MS (m/z): 368 (M + Na).

(E)-*N*-(4-(4-fluorophenyl)but-3-en-2-yl)-4-methylbenzenesulfonamide (Table-2, entry 11): IR (neat, cm^{-1}): 3236, 2969, 1599, 1509, 1434, 1325, 1226, 1093, 978. ^1H NMR (300 MHz, $CDCl_3$): δ 1.26 (d, 3H, *J* = 6.8 Hz), 2.36 (s, 3H), 4.01 - 4.09 (m, 1H), 4.86 (d, 1H, *J* = 7.3 Hz), 5.74 (dd, 1H, *J* = 6.8 Hz, 15.9 Hz), 6.25 (d, 1H, *J* = 15.9 Hz), 6.93 (d, 2H, *J* = 8.6 Hz), 7.09 (d, 2H, *J* = 8.6 Hz), 7.20 (d, 2H, *J* = 8.1 Hz), 7.73 (d, 2H, *J* = 8.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.4, 21.8, 51.6, 115.2 (d, *J* = 21.9 Hz), 127.3, 127.8 (d, *J* = 8.7 Hz), 129.2, 129.4, 130.1, 132.4, 142.7, 160.5, 163.8. ESI MS (*m/z*): 342 (M + Na).

***N*-(4-chloro-benzyl)-benzenesulfonamide (Table-3, entry 1):** IR (KBr, ν_{max}, cm^{-1}): 3452, 2875, 1601, 1567, 1314, 1179, 1070, 829. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 4.08 (d, 2H, *J* = 6.3 Hz), 5.04 (t, 1H, *J* = 6.3 Hz), 7.09-7.26 (m, 3H), 7.44 - 7.57 (m, 4H), 7.82 (d, 2H, *J* = 8.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 47.04, 127.02, 127.63, 127.74, 128.50, 129.58, 143.3. ESI-MS (*m/z*): 281(M+H).

***N*-(4-chloro-benzyl)-2,4,6-triisopropyl-benzenesulfonamide (Table-3, entry 2):** IR (KBr, ν_{max}, cm^{-1}): 3312, 2958, 1603, 1567, 1322, 1174, 1092, 829, 656. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.25 (d, 18H, *J* = 6.8 Hz), 2.86-2.95 (m, 3H), 4.10 (d, 2H, *J* = 6.0 Hz), 4.53(t, 1H, *J* = 6.0 Hz), 7.14 (d, 2H, *J* = 7.5 Hz), 7.22 (d, 2H, *J* = 8.3 Hz), 7.25 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 23.62, 24.87, 29.67, 34.16, 46.33, 123.79, 128.81, 129.37, 132.28, 133.78, 138.05, 150.24, 153.02. ESI-MS (*m/z*): 430 $(M+Na)^+$.

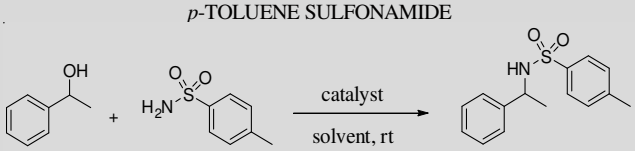
(E)-2,4,6-triisopropyl-*N*-(4-phenylbut-3-en-2-yl)-benzenesulfonamide (Table- 3, entry 4): IR (neat, ν_{max}, cm^{-1}): 3306, 2962, 1598, 1457, 1315, 1147, 1065, 966. ^1H NMR (300 MHz, $CDCl_3$): δ 1.22 (d, 12H, *J* = 6.6 Hz), 1.27 (d, 6H, *J* = 6.6 Hz), 1.33 (d, 3H, *J* = 6.6 Hz), 2.80-2.89 (m, 1H), 4.08-4.24 (m, 3H), 4.36 (d, 1H, *J* = 6.6 Hz), 5.82 (dd, 1H, *J* = 6.6 Hz, 15.8 Hz), 6.28 (d, 1H, *J* = 15.8 Hz), 7.03-7.07 (m, 4H), 7.14-7.19 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.9, 23.5, 24.6, 24.9, 29.6, 34.1, 51.4, 123.6, 126.2, 127.6, 128.4, 130.3, 133.8, 136.2, 149.8, 152.5. ESI MS (*m/z*): 436 (M + Na).

RESULTS AND DISCUSSION

In our initial studies, various palladium catalysts in combination with different solvents were investigated using 1-phenylethanol and *p*-toluene sulfonamide as model substrates (Table-1). The reaction conditions were optimized and the best conditions were found to be 2 mol % of Pd/Fe_3O_4 catalyst and nitromethane as a solvent (Table-1, entry 1). By virtue of these optimized conditions, the reaction afforded the desired product in 86 % yield. Reactions with other palladium catalysts such as $Pd(OAc)_2$ and Pd/C generate the desired product in low to moderate yields (Table-1, entries 2 and 3). However, the reaction with $PdCl_2$ gave the product in good yield (Table-1, entry 4). Subsequently, the reaction condition was optimized by employing different solvents, wherein various solvents were examined and was found that all of them had negative influence on the reaction to different degrees except toluene, where the product was formed in good yield (Table-1, entries 5-9).

Subsequently, on the basis of the optimized reaction conditions, the scope of this Pd/Fe_3O_4 catalyzed direct sulfamidation of several structurally diverse benzylic alcohol and allylic alcohol with *p*-toluene sulfonamide was explored and the results are summarized in Table-2. In general, the reaction proceeded efficiently with 1-phenylethanol, benzhydrol and gave the products in good to excellent yields (Table-2, entries 1 and 2). With these encouraging results in hand, we

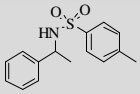
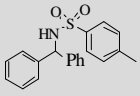
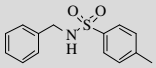
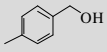
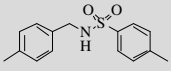
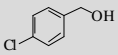
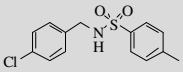
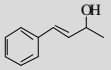
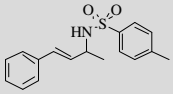
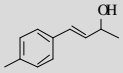
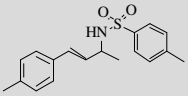
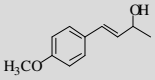
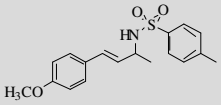
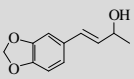
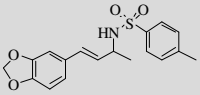
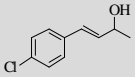
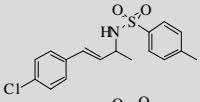
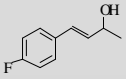
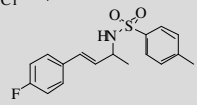
TABLE-1
SCREENING OF VARIOUS CATALYSTS AND SOLVENTS FOR DIRECT SULFAMIDATION OF 1-PHENYLETHANOL WITH *p*-TOLUENE SULFONAMIDE



Entry	Catalyst	Solvent	Yield (%)
1	Pd/Fe_3O_4	nitromethane	86
2	$Pd(OAc)_2$	nitromethane	30
3	Pd/C	nitromethane	45
4	$PdCl_2$	nitromethane	65
5	Pd/Fe_3O_4	toluene	80
6	Pd/Fe_3O_4	1,4-dioxone	34
7	Pd/Fe_3O_4	dichloromethane	20
8	Pd/Fe_3O_4	THF	15
9	Pd/Fe_3O_4	acetonitrile	35

[a]Reaction conditions: 1-phenylethanol (1 mmol), tosylamide (1.2 mmol), catalyst (2 mol %) solvent (3 mL)

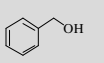
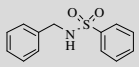
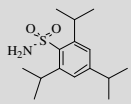
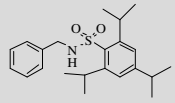
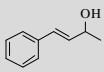
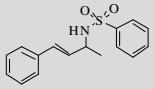
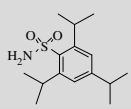
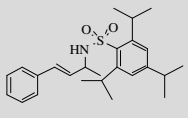
TABLE-2
DIRECT SULFAMIDATION OF DIFFERENT BENZYLIC AND ALLYLIC ALCOHOLS WITH p-TOLUENE SULFONAMIDE USING MAGNETICALLY RECOVERABLE Pd/Fe_3O_4

Entry	Alcohol	Product	T (ºC)	Time (h)	Yield (%)
1			30	4	86
2			30	3	95
3			80	6	74
4			80	6	80
5			80	6	78
6			30	4	90
7			30	4	85
8			30	4	82
9			30	4	84
10			30	4	91
11			30	4	87

[a]Reaction conditions: alcohol (1 mmol), tosylamide (1.2 mmol), Pd/Fe_3O_4 (2 mol % of Pd), nitromethane (3 mL)

subsequently set out to explore the scope of various benzyl alcohols (Table-2). In this study three different benzyl alcohols transformed into their corresponding benzyl sulfonamides in good yields (Table-2, entries 3-5). In further experiments, with regard to the importance of allylic amines[18-25], we investigated the amination of different allylic alcohols which showed similar reactivity as benzhydrols and the desired products were obtained in good to excellent yields (Table-2). Among the different allylic alcohols used, the unsubstituted and chloro, fluoro substituted allylic alcohols more reactive when compared to methyl, methoxy and 1,3-dioxole substituted allylic alcohols (Table-2, entries 6-11). Furthermore, the scope of the reaction with respect to sulfonamide substrate was also examined (Table-3). Both benzenesulfonamide and 2,4,6-triisopropyl-benzene sulfonamides were equally effective for direct sulfamidation and gave the corresponding benzyl amines in good yield (Table-3, entries 1 and 2). The reaction was equally effective for the sulfamidation of allylic alcohols and gave the expected allylic amines in excellent yield (Table-3, entries 3 and 4).

TABLE-3
DIRECT SULFAMIDATION OF BENZYLIC AND ALLYLIC ALCOHOLS WITH SULFONAMIDES USING MAGNETICALLY RECOVERABLE Pd/Fe_3O_4.

Entry	Alcohol	Sulfonamide	Product	T (ºC)	Time (h)	Yield (%)
1				90	6	86
2				90	6	95
3				30	4	74
4				30	4	80

[a]Reaction conditions: alcohol (1 mmol), sulfonamide (1.2 mmol), Pd/Fe_3O_4 (2 mol % of Pd), nitromethane (3 mL)

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