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N-Acyl-*N*-(4-chlorophenyl)-4-nitrobenzenesulfonamides: highly selective and efficient reagents for acylation of amines in water

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Abstract: A variety of *N*-acyl-*N*-(4-chlorophenyl)-4-nitrobenzenesulfonamides (**1a–e**) were synthesized in one pot from 4-chloroaniline under solvent-free conditions and have been developed as chemoselective N-acylation reagents. Selective protection of primary amines in the presence of secondary amines, acylation of aliphatic amines in the presence of aryl amines, and monofunctionalization of primary-secondary diamines as well as selective N-acylation of amino alcohols using these reagents are described. All of the acylation reactions were carried out in water as a green solvent. High stability and easy preparation of these acylating reagents are other advantages of this method.

Keywords: green chemistry; *N*-acyl-*N*-arylsulfonamide; selective acylation; water.

1 Introduction

Acylation of amines is of enormous interest in organic synthesis because it provides a useful and efficient protection protocol in a multistep synthesis process [1]. Many of chemical reactions involved in the synthesis of drugs frequently use acylation reactions. Acylation of amines are usually done by carboxylic acid anhydrides or chlorides in the presence of an acid or base catalyst in a suitable organic solvent [2, 3]. Selective acylation of amino groups in the presence of other functional groups that can be acylated by carboxylic acid anhydrides or chlorides has great practical utility [4–6]. A variety of reagents has been developed by devising a leaving group for the above purpose [7]. Acetylation of amines using a *N*-methoxydiacetamide [8], N-formylation using *N*-formylbenzotriazole [9], trifluoroacetylations with ethyl trifluoroacetate [10, 11], using *N*-acetyl-*N*-acyl-3-aminoquinazolinones for acetylating of primary amines [12], and application of (trifluoroacetyl)benzotriazole as trifluoroacetylation reagent [13] are some of the reagents and methods for chemoselective acylation of amines. Murakami and coworkers have synthesized *N*-acyl-*N*-(pentafluorophenyl) methanesulfonamides and have used them as chemoselective N-acylation reagents [14]. They have shown that a reagent bearing a bulky leaving group can exhibit sufficiently good chemoselectivity. The low stability of acylating agents, limited application, and the use of organic solvent are some of the disadvantages of these methods.

The design of chemical transformations with low environmental impact is recognized by both industry and academic research as increasingly important. In this context, the development of reactions occurring in nontoxic solvents is highly desirable [15, 16]. The application of water as an inexpensive, readily available, and environmentally benign alternative to organic solvents has developed into a highly active field of research addressing current requirements in synthetic chemistry [17–19].

In continuation of our research on the acylation reactions [20–23], we wish to report here the synthesis of a series of new acylating reagents, which are useful for the chemoselective acylation of amino groups of compounds that possess both amino and other groups in water.

2 Results and discussion

2.1 Synthesis of acylating reagents

At first, we decided to search for a versatile synthon to which various acyl groups could be introduced. We chose

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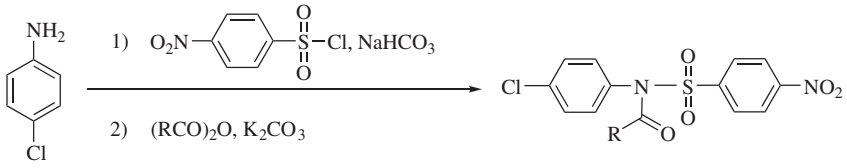


R = CH_3 (**1a**), n-C_3H_7 (**1b**), n-C_4H_9 (**1c**), n-C_5H_{11} (**1d**), Ph (**1e**)

Scheme 1: Synthesis of *N*-acyl-*N*-(4-chlorophenyl)-4-nitrobenzenesulfonamides (**1a–e**).

to focus on the use of *N*-(4-chlorophenyl)-4-nitrobenzenesulfonamide as a precursor of various N-acylation reagents. This sulfonamide is expected to behave as a bulky leaving group containing a strongly electron-withdrawing substituent on the benzene rings including nitro and chloro groups. This sulfonamide was synthesized from 4-chloroaniline and 4-nitrobenzenesulfonyl chloride in the presence of anhydrous $NaHCO_3$ under solvent-free conditions in high yield and purity (Scheme 1) [24]. Then, *N*-(4-chlorophenyl)-4-nitro-benzenesulfonamide was reacted with a carboxylic acid anhydride in the presence of anhydrous K_2CO_3 under solvent-free conditions. The reactions were completed very fast and the corresponding *N*-acyl-*N*-(4-chlorophenyl)-4-nitrobenzenesulfonamides **1a–e** were obtained in high yields and purity. Also, these *N*-acyl-*N*-arylsulfonamides could be prepared in one pot directly from 4-chloroaniline without the need to isolate *N*-(4-chlorophenyl)-4-nitro-benzenesulfonamide.

Several structurally varied carboxylic acid anhydrides underwent clean and remarkably fast N-acylation reaction (Table 1). The aliphatic anhydride with a long chain, like hexanoic anhydride (Table 1, entry 4, compound **1d**), could be used as effectively as one with a short chain. Comparison between the aliphatic and benzoic anhydride show that aliphatic anhydrides are more reactive than benzoic anhydride. It was found that the reaction between *N*-(4-chlorophenyl)-4-nitrobenzenesulfonamide, and benzoic anhydride produces *N*-benzoyl-*N*-(4-chlorophenyl)-4-nitrobenzenesulfonamide in 50 % yield after 10 h under solvent-free conditions (Table 1, entry 5, compound **1e**). To overcome this problem, the reaction was done in acetone as solvent. The procedure consists of the addition of benzoic anhydride to a mixture of *N*-(4-chlorophenyl)-4-nitrobenzenesulfonamide and K_2CO_3 in acetone. By this method, the product was obtained in 85 % yield after 4 h in high purity (Table 1, entry 6, compound **1e**). Also, it should be mentioned that these reactions were scalable and all of the *N*-acyl-*N*-(4-chlorophenyl)-4-nitrobenzenesulfonamides **1a–e** were synthesis on 20-mmol scales as well as 2-mmol scales.

Table 1: Synthesis of *N*-acyl-*N*-(4-chlorophenyl)-4-nitrobenzenesulfonamides **1a–e** (Scheme 1).[a]

Entry	R	Compound number	Time, min	Yield[b], %	M.p., °C
1	CH_3	**1a**	95	95	180–184
2	C_3H_7	**1b**	95	95	183–185
3	C_4H_9	**1c**	100	90	152–154
4	C_5H_{11}	**1d**	100	90	114–116
5	Ph	**1e**	600	50	134–136
6[c]	Ph	**1e**	240	85	134–136

[a]Reaction conditions: room temperature, K_2CO_3, solvent-free conditions. [b]Isolated yields. [c]The reaction was run in acetone.

2.2 Acylation of aromatic and aliphatic amines

First, to find the best conditions for the acylation of different amines using these novel acylating reagents, a number of reactions were performed. In our initial study, the acylation of *p*-anisidine with *N*-acetyl-*N*-(4-chlorophenyl)-4-nitrobenzenesulfonamide (**1a**) as a model reaction was carried out in different solvents including water, acetonitrile, *n*-hexane, and also under solvent-free conditions at different temperatures (Table 2).

It was found that the reaction at room temperature leads to the corresponding product in low yields. So the reactions were performed at higher temperature (60–80 °C). The best result was achieved when the reaction was performed in H_2O and acetonitrile at 80 °C. Based on this, water was selected as the best solvent for further study because the reaction was completed faster and the product was obtained in higher yield. Also, water is a green solvent in comparison with organic solvents. It should be mentioned that the reaction did not proceed under solvent-free conditions even after vigorous stirring for 6 h. The effect of base on the reaction was also studied in the acylation of *p*-anisidine in the presence of K_2CO_3, $NaHCO_3$, KOH, and also in the absence of base in water at 80 °C. The reaction did not proceed in the absence of base after 6 h. In the presence of K_2CO_3, $NaHCO_3$, and KOH, the

Table 2: Acetylation of *p*-anisidine with (**1a**) under different conditions.[a]

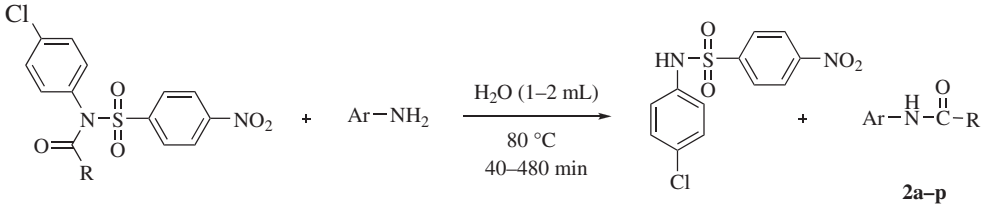
Entry	Solvent, mL	Temperature, °C	Time, min	Yield, %
1	–	25	240	0
2	–	40	240	10
3	–	60	240	15
4	Water (5)	25	360	0
5	Water (5)	40	150	10
6	Water (5)	60	150	15
7	Water (5)	80	40	75
8	Water (2)	80	40	88
8	Water (1)	80	40	93
8	Acetonitrile (5)	25	180	20
9	*n*-Hexane (5)	25	150	10
10	Acetonitrile (5)	80	150	80
11	*n*-Hexane (5)	60	150	20

[a]*N*-Acetyl-*N*-(4-chlorophenyl)-4-nitro-benzenesulfonamide (**1a**) (0.5 mmol), *p*-anisidine (1.5 mmol), and K_2CO_3 (2 mmol).

corresponding amide was obtained in 95, 80, and 50 % yield, respectively, after 40 min. When KOH was used as base, the acylating reagent hydrolyzed more easily, which may be the reason for the lower yield of the obtained amide. On the basis of these results, K_2CO_3 was selected as a green base for further study.

To demonstrate the generality and scope of this method, the acylation of different aliphatic and aromatic amines was studied using these new acylating reagents in water. It was observed that both aliphatic and aromatic amines gave the corresponding amides in good to excellent yield (Tables 3 and 4, compounds **2a–p** and **3a–q**). As the results show, in the acylation of aromatic amines, electronic and steric factors play a significant role in the reaction. Aromatic amines with electron-donating groups such as Me and MeO were acylated in a shorter reaction time, in comparison with aromatic amines containing electron-withdrawing groups such as Cl (e.g. Table 3, entries 2 and 4, compounds **2b** and **2d**). Aromatic amines with strongly electron-withdrawing group such as NO_2 did not react at all. Also, increasing the steric hindrance at the *ortho* position of amino group leads to a substantial decrease in yield (Table 3, entries 5, 6, and 7, compounds **2e**, **2f**, and **2g**). It is significant to note that the reaction of secondary amines with acylating reagent did not proceed

Table 3: Acylation of aromatic amines with different acylating reagents (**1a–e**) in water[a].

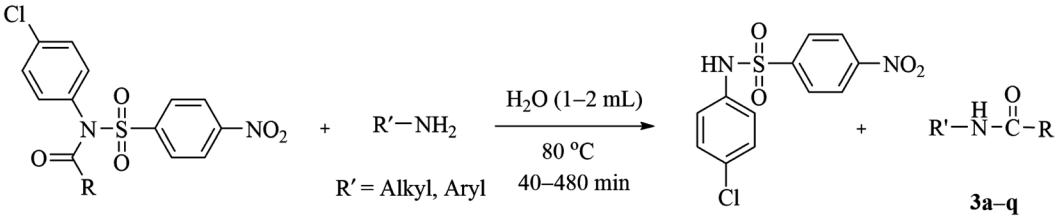


R = CH_3 (**1a**), *n*-C_3H_7 (**1b**), *n*-C_4H_9 (**1c**), *n*-C_5H_{11} (**1d**), Ph (**1e**)

Entry	Amines	Product	Compound number	M.p. (reported [ref.])	Time, min	Yield[b], %
1	Aniline	*N*-Phenylacetamide	**2a**	110–112 (114 [25])	180	87
2	4-Methoxyaniline	*N*-(4-Methoxyphenyl)acetamide	**2b**	131–133 (145–147 [4])	40	95
3	*p*-Toluidine	*N*-(4-Methylphenyl)acetamide	**2c**	152–154 (149–151 [25])	100	91
4	4-Chloroaniline	*N*-(4-Chlorophenyl)acetamide	**2d**	176–178 (178 [4])	340	85
5	2-Methoxyaniline	*N*-(2-Methoxyphenyl)acetamide	**2e**	88–90 (86–87 [4])	280	55
6	*o*-Toluidine	*N*-(2-Methylphenyl)acetamide	**2f**	105–108 (109 [25])	360	62
7	2-Chloroaniline	*N*-(2-Chlorophenyl)acetamide	**2g**	89–90 (88–90 [25])	420	20
8	*N*-Ethylaniline	*N*-Ethyl-*N*-phenylacetamide	**2h**	51–53 (50 [26])	480	10
9	4-Methoxyaniline	*N*-(4-Methoxyphenyl)butyramide	**2i**	82–86 (78–80 [27])	60	92
10	4-Methoxyaniline	*N*-(4-Methoxyphenyl)pentanamide	**2j**	83–86 (83–85 [28])	60	88
11	4-Methoxyaniline	*N*-(4-Methoxyphenyl)hexanamide	**2k**	84–86 (84–86 [29])	70	85
12	4-Methoxyaniline	*N*-(4-Methoxyphenyl)benzamide	**2l**	152–154 (157 [29])	85	90
13	*p*-Toluidine	*N*-(4-Methylphenyl)butyramide	**2m**	74–75 (74–76 [30])	110	87
14	*p*-Toluidine	*N*-(4-Methylphenyl)pentanamide	**2n**	68–72 (71–72 [30])	140	80
15	*p*-Toluidine	*N*-(4-Methylphenyl)hexanamide	**2o**	72–74 (74–75 [30])	140	80
16	*p*-Toluidine	*N*-(4-Methylphenyl)benzamide	**2p**	154–157 (158–159 [30])	155	85

[a]Reaction conditions: aromatic amine (1.5 mmol), acylating reagent (**1a–e**) (0.5 mmol), K_2CO_3 (2 mmol), H_2O (1–2 mL), 80 °C. [b]Isolated yields.

Table 4: Acylation of aliphatic amines with different acylating reagents (**1a–e**) in water.[a]



R = CH_3 (**1a**), *n*-C_3H_7 (**1b**), *n*-C_4H_9 (**1c**), *n*-C_5H_{11} (**1d**), Ph (**1e**)

Entry	Amines	Product	Compound Number	M.p. (reported [ref.])	Time, min	Yield,[b] %
1	Cyclohexanamine	*N*-Cyclohexylacetamide	**3a**	104–106 (101–103 [4])	15	80
2	Hexylamine	*N*-Hexylacetamide	**3b**	Oil (106, 20 Torr [31])	12	81
3	Benzylamine	*N*-Benzylacetamide	**3c**	56–58 (59–61 [4])	10	85
4	2-Phenylethanamine	*N*-Phenethylacetamide	**3d**	152–155 (158–160 [4])	5	89
5	Cyclohexanamine	*N*-Cyclohexylbutyramide	**3e**	66–68 (66–67 [32])	10	83
6	Benzylamine	*N*-Benzylbutyramide	**3f**	42–44 (41–44 [33])	5	89
7	Cyclohexanamine	*N*-Cyclohexylpentanamide	**3g**	54–56 (68 [32])	10	84
8	Hexylamine	*N*-Hexylpentanamide	**3h**	Oil (164–166, 13 Torr [34])	6	86
9	Benzylamine	*N*-Benzylpentanamide	**3i**	50–52 (49–52 [35])	7	89
10	Cyclohexanamine	*N*-Cyclohexylhexanamide	**3j**	72–74 (72–73 [34])	15	86
11	Hexylamine	*N*-Hexylhexanamide	**3k**	Oil (168–170, 13 Torr [34])	5	82
12	Benzylamine	*N*-Benzylhexanamide	**3l**	56–58 (54–55 [36])	7	90
13	2-Phenylethanamine	*N*-(2-Phenylethyl)hexanamide	**3m**	40–42 (38–41 [34])	5	95
14	Cyclohexanamine	*N*-Cyclohexylbenzamide	**3n**	147–149 (149.5 [32])	35	81
15	Hexylamine	*N*-Hexylbenzamide	**3o**	40–42 (46–47 [37])	7	95
16	Benzylamine	*N*-Benzylbenzamide	**3p**	106–108 (106–108 [35])	15	92
17	2-Phenylethanamine	*N*-(2-Phenylethyl)benzamide	**3q**	115–117 (119–120 [38])	30	88

[a]Reaction conditions: aliphatic amines (0.75 mmol), acylating reagent (**1a–e**) (0.5 mmol), K_2CO_3 (1 mmol), H_2O (1 mL), 80 °C. [b]Isolated yields.

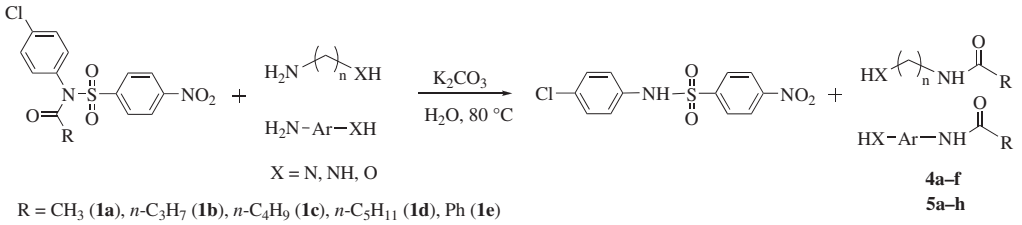
considerably under similar conditions even after 480 min, which may be due to unfavorable steric and electronic effects on nitrogen (Table 3, entry 8, compound **2h**). Also, the results showed that increased steric hindrance on the acylating reagents leads to increased reaction time and decreased yield of product (Table 3, entries 9–16, compounds **2i–p**).

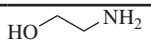
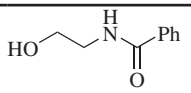
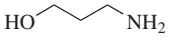
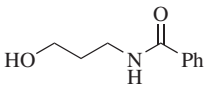
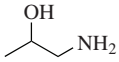
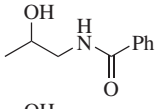
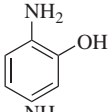
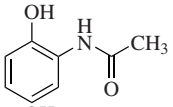
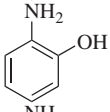
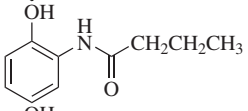
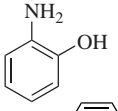
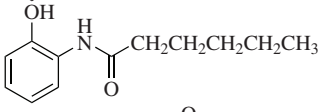
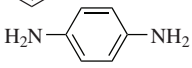
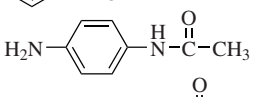
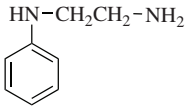
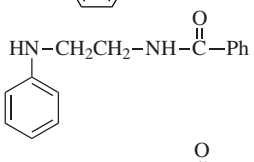
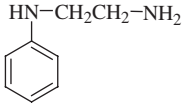
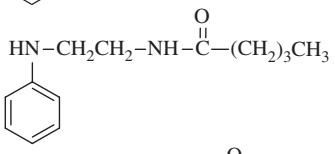
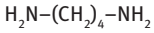
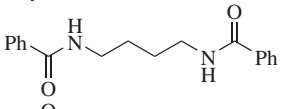
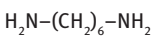
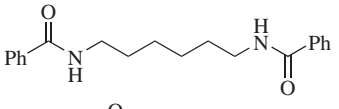
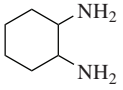
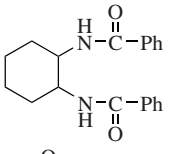
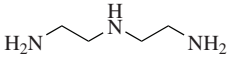
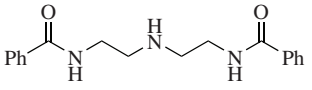
Then, the change of the substrate from aryl amines to alkyl amines was studied. As it was shown in Table 4 (compounds **3a–q**), all of the used primary aliphatic amines were reacted with different acylating reagents in short reaction time (3–35 min), and the corresponding amides were obtained in high to excellent yield (80–95 %).

2.3 Chemoselective acylation of amino alcohols and diamines

During the course of this study, we have shown the chemoselectivity of this method for the acylation of amino alcohols and diamines using these acylating reagents in water. As it is shown in Table 5 (compounds **4a–f** and **5a–g**), several aliphatic and aromatic amino alcohols and diamines were acylated with different acylating reagents in water, and the corresponding amides were obtained in high to excellent yield (74–98 %). The N-acylation of amino phenols was achieved in moderate to good yield, whereas hydroxyl groups remained unaffected under the reaction conditions (Table 5, entries 1–6, compounds **4a–f**). Also, the results show that the amino alcohols were acylated faster than amino phenols and the corresponding amides were obtained in higher yield. Selective monoacylation of aromatic diamines in water using these acylating reagents was also studied. The reaction of 1,4-benzenediamine with *N*-acetyl-*N*-(4-chlorophenyl)-4-nitrobenzene-sulfonamide lead to *N*-(4-aminophenyl)acetamide in 86 % yield (Table 5, entry 7, compound **5a**), and there was no diacylated product in the reaction mixture. Then, acylation of *N*-phenyl-ethylenediamine as an aliphatic-aromatic diamine was studied. The acylation reaction occurred selectively on the aliphatic amino group, and *N*-(2-(phenylamino)ethyl)-amides were obtained in 87–90 % yield (Table 5, entries 8 and 9, compounds **5b** and **c**). Finally, aliphatic diamines were acylated with this

Table 5: Acylation of diamines and amino alcohols or amino phenols with different acylating reagents (**1a–e**) in water.[b]



Entry	Diamine or amino alcohol	Product	Compound number	M.p. (reported [ref.])	Time, min	Yield,[a] %
1			**4a**	62–64 (56–58 [39])	25	97
2			**4b**	57–59 (56–58 [39])	20	98
3			**4c**	58–60 (60–63 [39])	20	92
4			**4d**	208–210 (207–209 [4])	30	86
5			**4e**	84–86 (81 [40])	120	65
6			**4f**	76–78 (74 [40])	180	65
7			**5a**	155–157 (164–165 [41])	120	86
8[c]			**5b**	124–126 (123–124 [42])	40	90
9[c]			**5c**	109–112	10	87
10			**5d**	172–174 (175–176 [43])	15	74
11			**5e**	158–162 (164–165 [44])	10	75
12			**5f**	258–260 (256–257 [45])	30	78
13			**5g**	140–142 (135–136 [46])	15	77

[a]Isolated yields after purification. [b]Reaction conditions: diamines or amino alcohols (0.5 mmol), acylating reagent (**1a–e**) (0.5 mmol), K_2CO_3 (1 mmol for diamines and 3 mmol for amino alcohols or amino phenols), H_2O (1–2 mL), 80 °C. [c]Reaction conditions: diamines (0.75 mmol), acylating reagent (**1a–e**) (0.5 mmol), K_2CO_3 (1 mmol), H_2O (1–2 mL), 80 °C.

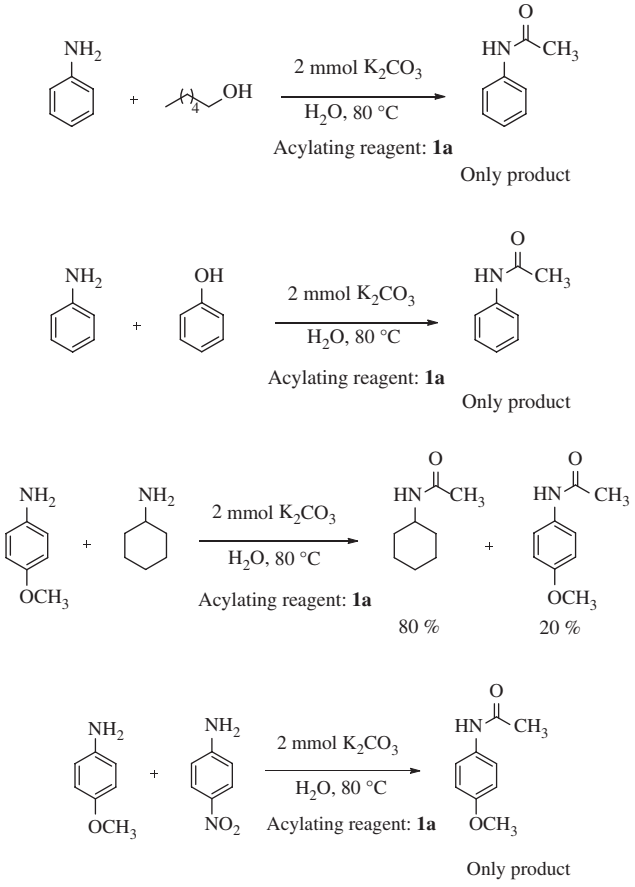
method. As it is shown in Table 5, primary diamines such as 1,6-hexanediamine and 1,2-cyclohexanediamine were acylated completely, and the diamides were obtained (Table 5, entries 11, 12, compounds **5e**, **5f**). Interestingly, acylation of *N*[1]-(2-aminoethyl)ethane-1,2-diamine containing both primary and secondary aliphatic amine with *N*-benzoyl-*N*-(4-chlorophenyl)-4-nitrobenzenesulfonamide occurred only on the primary amino group, and the corresponding diamine was obtained in 77 % yield after 15 min (Table 5, entry 13, compound **5g**).

The results of selective acylation of diamines and amino alcohols encouraged us to consider the selectivity of acylation of different amines in the presence of phenols and alcohols. Several reactions were carried out, and surprisingly, excellent selectivity was found (Scheme 2). For example, aromatic amines such as aniline can be converted into amide in the presence of phenol or aliphatic alcohol like 1-hexanol. Meanwhile, aliphatic amines were acylated selectively in the presence of aromatic amines. Also, the selective acylation of aromatic amines with electron-donating substituent in the presence of aromatic amines with electron-withdrawing group is possible with this method.

To investigate the reason for these chemoselectivity, the structure of synthesized acylating reagents were studied by density functional theory (DFT) calculations [47] using the program GAUSSIAN 98 [48]. The geometries of the acylating reagents were optimized using the DFT/B3LYP theory and a 6-31G (d,p) basis set. Vibrational frequency calculations were used to characterize all stationary points as minima (the number of imaginary frequencies [NIMAG] = 0). The calculated vibrational frequencies were found to be in good agreement with the experimentally recorded values. Figure 1 shows the optimized molecular structure of *N*-butyryl-*N*-(4-chlorophenyl)-4-nitrobenzenesulfonamide (**1b**) as an example, with its molecular structure belonging to point group symmetry C_1. The structural information for this compound is listed in Table 6. As this structure shows, the 4-chlorophenyl group is placed almost perpendicular to the plane of carbonyl and provides high steric bulkiness around this group. These results are supported by the experimental observations. Increasing the steric hindrance around the carbonyl group leads to an increase in acylation reaction time and a decrease of the product yield especially for poor and bulky nucleophiles.

2.4 Stability and reusability of acylating reagents

The special property of these new acylating reagents is their enormous stability. These compound can be stored in a bottle for a long time without any decomposition. As mentioned earlier, these reagents were used for



Scheme 2: Chemoselective acylation of amine and alcohol or phenol in the presence of K_2CO_3 in water at 80 °C.

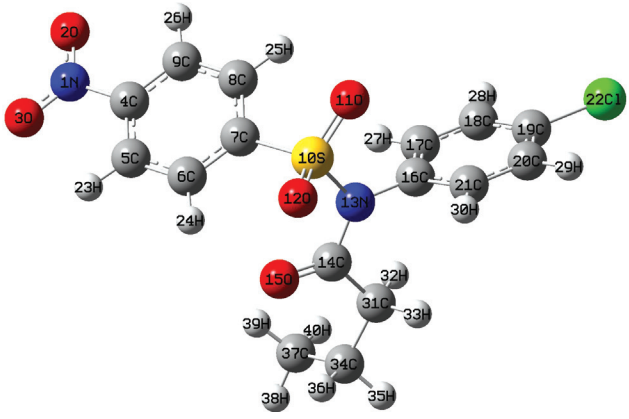


Fig. 1: The optimized structure of *N*-butyryl-*N*-(4-chlorophenyl)-4-nitrobenzenesulfonamide (**1b**).

Table 6: Bond lengths (Å), angles (deg), and dihedral angles (deg) of *N*-butyryl-*N*-(4-chlorophenyl)-4-nitrobenzenesulfonamide (**1b**) as obtained by DFT calculations.

Bond lengths		Angles		Dihedral angles	
N1–O2	1.22	O2–N1–O3	124.9	O11–S10–N13–C14	−179.8
Cl22–C19	1.75	O11–S10–O12	121.5	O12–S10–C7–C8	151.9
S10–O11	1.46	N13–C14–O15	120.5	C16–N13–C14–O15	−177.0
N13–C14	1.40	O15–C14–C31	123.1		
C14–O15	1.21	C14–C31–C34	112.8		
C31–C34	1.53	C31–C34–C37	113.7		
C31–H33	1.09				

the acylation of amines in alkaline hot water. So, the stability of these compounds was examined in water at 80 °C in the presence of K_2CO_3. It is interesting that after 6 h, <10 % of hydrolysis products were separated. Meanwhile, after acylation reaction, *N*-(4-chlorophenyl)-4-nitrobenzenesulfonamide can be separated from the reaction mixture almost completely and reused for the synthesis of the *N*-acyl-*N*-(4-chlorophenyl)-4-nitrobenzenesulfonamides **1a–e**.

3 Conclusion

In conclusion, an efficient approach was introduced for the synthesis of a series of new acylating reagents under solvent-free conditions. The chemoselective acylation of amino groups in diamines, amino alcohols, amino phenols, and also in the mixture of amine and alcohol or phenol in the presence of K_2CO_3 as a green base in water as an environmental friendly solvent was easily achieved by these new acylating agents. These acylating reagents are highly stable even in water at 80 °C. High yields of the products, simple experimental procedures, and the use of water as a green solvent are the other main advantages of this method.

4 Experimental section

All chemicals were purchased from Merck and Fluka. Infrared spectra were recorded on a Perkin-Elmer V IR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker (400 MHz) FT spectrometer in $CDCl_3$ and [D or d] DMSO. Chemical shifts δ are given in parts per million and coupling constants J in hertz. Column chromatography was performed using silica gel 60 (230–400 mesh). All reactions were conducted open to the atmosphere, and the yields refer to isolated products.

4.1 General procedure for the synthesis of *N*-acyl-*N*-(4-chlorophenyl)-4-nitrobenzene sulfomamides (1a–d)

4-Chloroaniline (2 mmol, 0.255 g) and anhydrous $NaHCO_3$ (1 g) were ground together into a fine powder, and 4-nitrobenzenesulfonyl chloride (2 mmol, 0.442 g) was added under vigorous stirring at room temperature. The progress of the reaction was followed by TLC until the conversion of amine was completed. The product showed one spot on TLC and was used in the second step without isolation. Carboxylic acid anhydrides (10 mmol of acetic anhydride, 4 mmol of butyric anhydride, 5 mmol of pentanoic anhydride and hexanoic anhydride) and anhydrous K_2CO_3 (1 g) were added, and the mixture was stirred vigorously at room temperature. The reaction was monitored by TLC. Upon completion of the reaction, water was added and the mixture was stirred for a few minutes. After filtration, washing with additional water and drying, the corresponding *N*-acyl-*N*-(4-chlorophenyl)-4-nitrobenzenesulfonamide (compounds **1a–d**) was obtained in 90–95 % yield with high purity and was used for the acylation reaction without purification.

4.1.1 *N*-(4-Chlorophenyl)-4-nitrobenzenesulfonamide

M.p. 180–184 °C. – IR (film): ν = 3269 (N–H), 1527, 1348, 1333 (SO_2), 1306, 1160 (SO_2), 561 (C–N) cm^{-1}. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.65 (s, 1 H, NH), 7.06 (d, J = 8.8 Hz, 2 H, Ar-H^8), 7.26–7.32 (m, 2 H, Ar-H^7), 7.95 (d, J = 8.8 Hz, 2 H, Ar-H^6), 8.30 (d, J = 8.8 Hz, 2 H, Ar-H^5). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 123.9 (C-8), 124.4 (C-7), 128.5 (C-6), 129.8 (C-5), 132.3 (C–Cl), 133.8 (C–NH), 144.3 (C–SO_2), 150.3 (C–NO_2).

4.1.2 *N*-Acetyl-*N*-(4-chlorophenyl)-4-nitrobenzenesulfonamide (1a)

M.p. 183–185 °C. – R_f (film): ν = 3139, 1719 (C=O), 1535, 1352 (SO_2), 1166 (SO_2), 553 (C–N) cm^{-1}. – ^{1}H NMR (400 MHz,

$CDCl_3$): δ = 1.92 (s, 3 H, CH_3), 7.23–7.30 (m, 2 H, Ar-H[6]), 7.53 (d, J = 8.8 Hz, 2 H, Ar-H[8]), 8.25 (d, J = 8.8 Hz, 2 H, Ar-H[7]), 8.42 (d, J = 8.8 Hz, 2 H, Ar-H[9]). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.9 (C-10), 124.0 (C-9), 130.5 (C-8), 130.6 (C-7), 131.0 (C-6), 134.5 (C–Cl), 136.9 (C–N), 144.2 (C–SO_2), 150.8 (C–NO_2), 169.9 (C=O). –$C_{14}H_{11}ClN_2O_5S$: calcd. C 47.40, H 3.13, N 7.90; found C 47.21, H 3.05, N 8.01.

4.1.3 *N*-Butyryl-*N*-(4-chlorophenyl)-4-nitrobenzenesulfonamide (1b)

M.p. 152–154 °C. – R_f (film): ν = 3103, 1723 (C=O), 1535, 1374 (SO_2), 1146, 1185 (SO), 567 (C–N) cm^{-1}. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.81 (t, J = 7.2 Hz, 3 H, CH_3), 1.56 (sext, J = 7.2 Hz, 2 H, CH_2[11]), 2.02 (t, J = 7.2 Hz, 2 H, CH_2[10]), 7.24 (d, J = 8.4 Hz, 2 H, Ar-H[6]), 7.53 (d, J = 8.4 Hz, 2 H, Ar-H[9]), 8.26 (d, J = 8.4 Hz, 2 H, Ar-H[7]), 8.42 (d, J = 8.4 Hz, 2 H, Ar-H[8]). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.3 (C-12), 17.6 (C-11), 38.5 (C-10), 124.0 (C-9), 130.4 (C-8), 130.6 (C-7), 131.2 (C-6), 134.0 (C–Cl), 136.8 (C–N), 144.4 (C–SO_2), 150.7 (C–NO_2), 172.7 (C=O). – $C_{16}H_{15}ClN_2O_5S$: calcd. C 50.20, H 3.95, N 7.32; found C 50.31, H 3.85, N 7.41.

4.1.4 *N*-(4-Chlorophenyl)-*N*-pentanoyl-4-nitrobenzenesulfonamide (1c)

M.p. 144–146 °C. – R_f (film): ν = 3099, 1713 (C=O), 1531, 1376 (SO_2), 1186, 1159 (SO_2), 572 (C–N) cm^{-1}. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.80 (t, J = 6.8 Hz, 3 H, CH_3), 1.16–1.24 (m, 2 H, CH_2[12]), 1.46 (quint, J = 6.8 Hz, 2 H, CH_2[11]), 2.04 (t, J = 6.8 Hz, 2 H, CH_2[10]), 7.24 (d, J = 8.0 Hz, 2 H, Ar-H[6]), 7.53 (d, J = 8.0 Hz, 2 H, Ar-H[9]), 8.25 (d, J = 8.0 Hz, 2 H, Ar-H[7]), 8.41 (d, J = 8.0 Hz, 2 H, Ar-H[8]). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.6 (C-13), 21.8 (C-12), 26.1 (C-11), 36.4 (C-10), 124.0 (C-9), 130.4 (C-8), 130.6 (C-7), 131.1 (C-6), 134.0 (C–Cl), 136.8 (C–N), 144.4 (C–SO_2), 150.7 (C–NO_2), 172.8 (C=O). – $C_{17}H_{17}ClN_2O_5S$: calcd. C 51.45, H 4.32, N 7.06; found C 51.31, H 4.45, N 7.11.

4.1.5 *N*-(4-Chlorophenyl)-*N*-hexanoyl-4-nitrobenzenesulfonamide (1d)

M.p. 134–136 °C. – R_f (film): ν = 3103, 1723 (C=O), 1534, 1374 (SO_2), 1185, 1146 (SO_2), 567 (C–N) cm^{-1}. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.83 (t, J = 7.2 Hz, 3 H, CH_3), 1.1–1.26 (m, 4 H, 2 × CH_2[12,13]), 1.47–1.63 (m, 2 H, CH_2[11]), 2.03 (t, J = 7.6 Hz, 2 H, CH_2[10]), 7.24 (dd, J_1 = 6.4 Hz, J_2 = 3.2 Hz, 2 H, Ar-H[6]), 7.53 (dd, J_1 = 6.4 Hz, J_2 = 3.2 Hz, 2 H, Ar-H[9]), 8.26 (dd, J_1 = 5.2 Hz, J_2 = 2.0 Hz, 2 H, Ar-H[7]), 8.42 (dd, J_1 = 5.2 Hz, J_2 = 2.0 Hz, 2 H, Ar-H[8]). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.7 (C-14), 22.2 (C-13), 23.8 (C-12), 30.8 (C-11), 36.7 (C-10), 124.0 (C-9), 130.4 (C-8), 130.6 (C-7), 131.1 (C-6), 134.0 (C–Cl), 136.8 (C–N), 144.4 (C–SO_2), 150.7 (C–NO_2), 172.9 (C=O). – $C_{18}H_{19}ClN_2O_5S$: calcd. C 52.62, H 4.66, N 6.82; found C 52.51, H 4.49, N 6.80.

4.2 Synthesis of *N*-benzoyl-*N*-(4-chlorophenyl)-4-nitrobenzenesulfonamide (1e)

4-Chloroaniline (2 mmol, 0.255 g) and anhydrous $NaHCO_3$ (1 g) were ground together into a fine powder, and 4-nitrobenzenesulfonyl chloride (2 mmol, 0.442 g) was added under vigorous stirring at room temperature. The progress of the reaction was followed by TLC until the conversion of amine was completed. The product showed one spot on TLC and was used in the second step without isolation. Benzoic anhydride (2 mmol, 0.452 g), anhydrous K_2CO_3 (1 g), and acetone (10 mL) were added to the mixture and stirred at room temperature. Upon completion of the reaction, as it was shown by TLC, the solvent was evaporated, water was added, and the mixture was stirred for a few minutes. After filtration, washing with additional water, and drying, *N*-benzoyl-*N*-(4-chlorophenyl)-4-nitrobenzenesulfonamide (**1e**) was obtained in 85 % yield with high purity and was used for the acylation reaction without any purification. M.p. 206–208 °C. – R_f (film): ν = 3108, 1702 (C=O), 1533, 1372 (SO_2), 1176 (SO_2), 577 (C–N) cm^{-1}. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.11 (d, J = 8.4 Hz, 2 H, Ar-H[8]), 7.25 (d, J = 7.6 Hz, 2 H, Ar-H[9]), 7.28–7.35 (m, 3 H, H^{solvent}, Ar-H[11]), 7.40 (t, J = 7.6 Hz, 1 H, Ar-H[6]), 7.48 (d, J = 7.6 Hz, 2 H, Ar-H[10]), 8.15 (d, J = 8.8 Hz, 2 H, Ar-H[12]), 8.40 (d, J = 8.8 Hz, 2 H, Ar-H[13]). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 123.9 (C-13), 128.4 (C-12), 129.7 (C-11), 129.8 (C-10), 130.8 (C-9), 131.1 (C-8), 132.3 (C–Cl), 132.7 (C-6), 135.40 (C-5), 135.8 (C–N), 143.4 (C–SO_2), 150.7 (C–NO_2), 169.7 (C=O). – $C_{19}H_{13}ClN_2O_5S$: calcd. C 54.75, H 3.14, N 6.72; found C 54.61, H 3.25, N 6.65.

4.2.1 General procedure for the acylation of aromatic and aliphatic amines

A mixture of the acylating reagents **1a–e** (0.5 mmol), aryl amine (1.5 mmol), or alkyl amine (0.75 mmol) and K_2CO_3 (2 mmol for aromatic amines and 1 mmol for aliphatic amines) was stirred in H_2O (1–2 mL) at 80 °C for the appropriate period of time. After completion of the reaction as indicated by TLC, the reaction mixture was acidified with 5 % HCl and extracted with EtOAc (50 mL) and water (10 mL). The combined organic layer was concentrated

in vacuo and purified by column chromatography on silica gel to afford the pure product (compounds **2a–p** and **3a–q**).

4.2.2 General procedure for the acylation of diamines, amino alcohols, and amino phenols

A mixture of the acylating reagents **1a–e** (0.5 mmol), diamines or amino alcohol (0.5 mmol), and K_2CO_3 (1 mmol for diamines and 3 mmol for amino alcohol or amino phenol) was stirred in H_2O (1–2 mL) at 80 °C for the appropriate period of time. The progress of the reaction was monitored by TLC. Upon completion of the reaction, the solvent of the mixture was evaporated. Then, acetone (10 mL) was added and K_2CO_3 was filtered off and washed with additional solvent (20 mL). After evaporation of the solvent, the crude product was purified by column chromatography on silica gel to afford the pure products (compounds **4a–f** and **5a–g**).

4.3 Spectral data of new amides from diamines

4.3.1 *N*-(2-(Phenylamino)ethyl)benzamide (5b)

M.p. 124–128 °C. – R_f (film): ν = 3375, 3027, 1630 (C=O), 1600, 1576, 1524, 1326, 1132, 741, 712, 691 cm^{-1}. – ^1H NMR (400 MHz, $CDCl_3$): δ = 3.42 (t, J = 6.0 Hz, 2 H, CH_2^{10}), 3.70–3.76 (m, 3 H, CH_2^{11}, NH), 6.66–6.72 (m, 3 H, Ar-H^9, NHCO), 6.76 (t, J = 7.6 Hz, 1 H, Ar-H^8), 7.21 (t, J = 7.6 Hz, 2 H, Ar-H^5), 7.43 (t, J = 7.6 Hz, 2 H, Ar-H^6), 7.52 (t, J = 7.6 Hz, 1 H, Ar-H^4), 7.78 (d, J = 7.2 Hz, 2 H, Ar-H^7). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 39.7 (C–NHCO), 44.0 (C–NH), 112.9 (C-9), 117.8 (C-8), 126.9 (C-7), 128.6 (C-6), 129.4 (C-5), 131.6 (C-4), 134.2 (C-3), 147.8 (C-2), 168.2 (C=O).

4.3.2 *N*-(2-(Phenylamino)ethyl)pentanamide (5c)

M.p. 109–112 °C. – R_f (film): ν = 3401, 2929, 1647 (C=O), 1603, 1647, 1512, 1259, 749, 692 cm^{-1}. – ^1H NMR (400 MHz, $CDCl_3$): δ = 0.93 (t, J = 7.6 Hz, 3 H, CH_3), 1.36 (sext, J = 7.6 Hz, 2 H, CH_2^{10}), 1.63 (quint, J = 7.6 Hz, 2 H, CH_2^9), 2.20 (t, J = 7.2 Hz, 2 H, CH_2^8), 3.30 (t, J = 7.2 Hz, 2 H, CH_2^6), 3.51–3.57 (m, 3 H, CH_2^7, NH), 5.88 (brs, 1 H, NHCO), 6.66 (d, J = 7.6, 2 H, Ar-H^5), 6.75 (t, J = 7.6 Hz, 1 H, Ar-H^4), 7.21 (t, J = 7.6 Hz, 2 H, Ar-H^3). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.8 (C-11), 22.4 (C-10), 27.8 (C-9), 36.5 (C-8), 39.0 (C–NHCO), 44.2 (C–NH), 112.8 (C-5), 117.8 (C-4), 129.3 (C-3), 147.8 (C-2), 174.0 (C=O).

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Graphical synopsis

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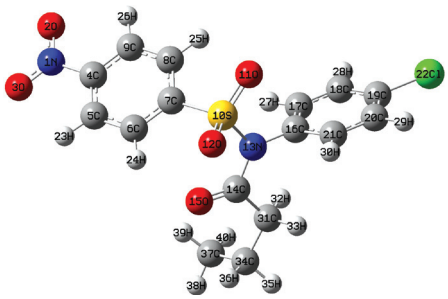
***N*-Acyl-*N*-(4-chlorophenyl)-4-nitrobenzenesulfonamides: highly selective and efficient reagents for acylation of amines in water**



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