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A facile amidation of chloroacetyl chloride using DBU

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Abstract : A facile one-pot process for the synthesis of amides from aromatic amines and chloroacetyl chloride has been developed using DBU. The method gave 75 to 95% yields in 3-6 h using tetrahydrofuran (THF) as a solvent at room temperature. The products have been characterized by mp, IR, ^{1}H NMR and elemental analysis.
Keywords: Amide bond formation, Aryl amines, chloroacetyl chloride, DBU, DABCO, THF.

Introduction

Amide functional group plays a vital role in organic synthesis.[1] A large number of natural and synthetic molecules possess this functional group. The synthetic chemists are always looking for better methods for the formation of amide bond.[2-6] The condensation of an amine or aniline with carboxylic acid or its derivatives is commonly employed method for amide bond formation.[2-6] The reported methods are not suitable for all the universally applicable substrate classes. We needed an efficient process to synthesize different N-aryl amides for a drug discovery program. The synthesized N-phenylacetamides, N-benzothiazol-2-ylacetamides and N-(4-phenylthiazol-2-yl)acetamides have great interest in recent years due to their wide role in the synthesis of biologically active compounds that exhibit pharmaceutical properties like analgesic activities,[7] $S1P_1$ receptor agonist,[8] A_2B adenosine receptor,[9] HIV-1 reverse transcriptase inhibitor,[10] anticancer activity,[11] antimicrobial and antituberculosis,[12-14] COX-2 inhibitors[15]. Several synthetic methodologies has been adopted for the synthesis of 2- chloroacetamide in solution phase using a various solvent with different bases such as TEA in DMF,[16] TEA in DCM,[8] toluene,[17] K_2CO_3 in benzene,[13] TEA in THF[18], TEA in dioxane.[15] However, in spite of their potential utility, many of these reported methods suffer from drawbacks such as harsh reaction conditions, long reaction times, unsatisfactory yields, tedious product isolation procedures and needs purification by column chromatography.[15-18] So the development of an improved protocol is of considerable interest. As a part of our ongoing effort towards the synthesis of biologically active compounds, we herein developed an efficient high yielding synthetic protocol for the synthesis of amides like N-phenylacetamides, N-benzothiazol-2-ylacetamide and N-(4-phenylthiazol-2-yl)acetamides.

Experimental

The chemicals used in the synthesis were purchased from reputed companies and used as received. The purities of the compounds and progress of the reactions were determined on silica-coated Al plates (Merck). Melting points were determined on a melting point apparatus and are uncorrected. IR (KBr) spectra were recorded using Perkin-Elmer FTIR spectrophotometer and the values are expressed as cm^{-1}. The ^{1}H NMR spectra were recorded on Joel Delta 400 MHz and Bruker Spectrospin spectrometer at 400 MHz using TMS as

an internal standard. The chemical shift values are recorded on δ scale and the coupling constants (J) are in Hz. Elemental analysis was performed on a Carlo Erba Model EA-1108 elemental analyzer.

General procedure for synthesis:

In a 50 mL round bottom flask, substituted aniline/amino thiazole (6 mmol) was dissolved in THF (5 ml). To this solution, DBU (1.2 mmol) was added. The reaction mixture was placed on freezing mixture of ice and salt & mechanically stirred for 15 min. To this reaction mixture, chloroacetyl chloride (6.1 mmol) was added from dropping funnel at such rate that the temperature does not rise beyond 5^{o}C. After all chloroacetyl chloride was added to the reaction mixture, it was stirred for 3-6 h at rt. The progress of reaction was monitored by TLC (Hexane: EtOAc; 7:3). After completion, the reaction mixture was poured into cold water. The compound was precipitated out. This was filtered and washed with water. The precipitate was dried and recrystallized by using ethanol as solvent. The product was obtained as solid powder.

N-benzothiazole-2-yl-2-chloroacetamide (10) - IR (cm^{-1}): 772, 1268, 1438, 1550, 1581, 1651, 1689, 2972, 3228; ^{1}H NMR (400 MHz, DMSO): δ 4.47 (2H, s, CH_2), 7.43-8.01 (4H, ArH), 12.72 (1H, NH, bs); Anal. calc. for $C_9H_7N_2OSCl$: C, 47.69; H, 3.11; N, 12.36; S, 14.15; found C, 47.59; H, 3.08; N, 12.21; S, 14.09.

2-chloro-N-(6-chlorobenzothiazole-2-yl)-acetamide (11) - IR (cm^{-1}): 781, 1275, 1378, 1554, 1595, 1645, 1692, 2945, 3248; ^{1}H NMR (400 MHz, DMSO): 4.46 (2H, s, CH_2), 7.35-8.05 (3H, m, ArH), δ 12.78 (1H bs, NH); Anal. calc. for $C_9H_6N_2OSCl_2$: C, 41.40; H, 2.32; N, 10.73; S, 12.28; found C, 41.23; H, 2.26; N, 10.68; S, 12.23.

2-chloro-N-(4-phenylthiazol-2-yl)acetamide (12) – IR (cm^{-1}): 575, 686, 722, 849, 1025, 1140, 1264, 1327, 1442, 1572, 1657, 3354; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.23 (2H s, CH_2), 6.75(1H s, CH Thiazole) 7.28-7.81(5H m, ArH), 10.20 (1H, bs NH); Anal. calc. for $C_{11}H_9N_2OSCl$: C, 52.28; H, 3.59; N, 11.08; S, 12.69; found C, 51.82; H, 3.23; N, 11.02; S, 12.36.

2-chloro-N-[4-(4-chlorophenyl)-thiazol-2-yl]-acetamide (13) – IR (cm^{-1}) : 593, 670, 761, 841, 1012, 1084, 1177, 1291, 1312, 1403, 1478, 1543, 1692, 3373; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.27 (2H, s, CH_2), 6.73 (1H, s, CH Thiazole), 7.35-7.37 (2H, d, J= 8.4 Hz, ArH), 7.72-7.74 (2H, d, J= 8.4 Hz, ArH), 9.75 (1H, bs, NH); Anal. calc. for $C_{11}H_8N_2OSCl_2$: C, 46.01; H, 2.81; N, 9.76; S, 11.17. found C, 44.23; H, 2.62; N, 9.56; S, 11.02;

2-chloro-N-[4-(4-fluorophenyl)-thiazol-2-yl]-acetamide (14) -IR (cm^{-1}): 519, 707, 831, 1067, 1161, 1266, 1488, 1576, 1662, 3362; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.25 (2H ,s, CH_2), 6.67 (1H, s, CH Thiazole), 7.06-7.10 (2H, d, J= 8.8 Hz, ArH), 7.74-7.78 (2H, d, J= 8.8 Hz, ArH), 9.34 (1H, bs, NH); Anal. calc. for $C_{11}H_8N_2OSFCl$: C, 48.80; H, 2.98; N, 10.35; S, 11.84; found C, 48.51; H, 2.70; N, 10.21; S, 11.34.

2-chloro-N-[4-(4-bromophenyl)-thiazol-2-yl]-acetamide (15) -IR (cm^{-1}): 521, 712, 843, 1072, 1268, 1515, 1586, 1675, 3472; ^{1}H NMR (400 MHz,$CDCl_3$): δ 4.12 (2H, s, CH_2), 6.69 (1H, s, CH Thiazole), 7.19-7.21 (2H, d, J= 7.6Hz ArH), 7.67-7.69 (2H, d, J= 7.6Hz, ArH), 9.04 (1H, bs, NH); Anal. calc. for $C_{11}H_8N_2OSBrCl$: C, 39.84; H, 2.43; N, 8.45; S, 9.67; found C, 39.78; H, 2.38; N, 8.41; S, 9.62.

2-chloro-N-(4-p-tolyl-thiazol-2-yl)-acetamide (16) -IR (cm^{-1}): 508, 700, 820, 974, 1070, 1140, 1268, 1328, 1426, 1567, 1699, 3320; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.40 (3H, s, CH_3), 4.20 (2H, s, CH_2), 7.15 (1H, s, CH Thiazole), 7.24-7.26 (2H, d, J= 6.8 Hz, ArH), 7.72-7.73 (2H, d, J= 6.8 Hz, ArH), 10.23 (1H, bs, NH); Anal. calc. for $C_{12}H_{11}N_2OSCl$: C, 54.03; H, 4.16; N, 10.50; S, 12.02; found C, 53.98; H, 4.10; N, 10.41; S, 11.96.

2-chloro-N-[4-(4-methoxyphenyl)-thiazol-2-yl]-acetamide (17) -IR (cm^{-1}): 534, 735, 843, 972, 1029, 1171, 1255, 1330, 1429, 1538, 1694, 3328; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.87 (3H s, OCH_3), 4.27 (2H, s, CH_2), 6.96-6.98 (2H, d, J= 8.4 Hz, ArH), 7.08 (1H, s, CH Thiazole), 7.76-7.78 (2H, d, J= 8.4 Hz, ArH), 9.93 (1H, bs, NH); Anal. calc. for $C_{12}H_{11}N_2O_2SCl$: C, 50.97; H, 3.92; N, 9.91; S, 11.34; found C, 50.51; H, 3.70; N, 9.41; S, 11.16.

2-chloro-N-[4-(4-nitrophenyl)-thiazol-2-yl]-acetamide (18) -IR (cm^{-1}): 532, 738, 854, 1038, 1180, 1265, 1345, 1436, 1542, 1560, 1678, 3315; ^{1}H NMR (400 MHz, DMSO): δ 4.27 (2H, s, CH_2), 7.41 (1H, s, CH Thiazole), 8.03-8.06 (2H, d, J= 8.8 Hz, ArH), 8.22- 8.24 (2H, J= 8.8 Hz, ArH.), 9.87 (1H, bs, NH); Anal. calc. for $C_{11}H_8N_3O_3SCl$: C, 44.38; H, 2.71; N, 14.11; S, 10.17; found C, 44.21; H, 2.60; N, 13.96; S, 10.06.

2-chloro-N-[4-(4-cyanophenyl)-thiazol-2-yl]-acetamide (19) -IR (cm^{-1}): 532, 738, 854, 1038, 1180, 1265, 1345, 1435, 1542, 1560, 1678, 3315; ^1H NMR (400 MHz, DMSO): δ 4.24 (2H, s, CH_2), 6.98 (1H, s, CH Thiazole), 7.44-7.46 (2H, d, J= 8.4 Hz, ArH), 7.92-7.93 (2H, d, J= 8.4 Hz, ArH), 9.84 (1H, bs, NH); Anal. calc. for $C_{12}H_8N_3OSCl$: C, 61.34; H, 4.58; N, 15.90; S, 18.19; found C, 63.51; H, 3.70; N, 19.41; S, 8.96.

2-chloro-N-[4-(3,4-dichlorophenyl)-thiazol-2-yl]-acetamide (20)-IR(cm^{-1}): 538, 746, 832, 1060, 1132, 1246, 1355, 1415, 1528, 1652, 3349; ^1H NMR (400 MHz, DMSO): δ 4.23 (2H, s, CH_2), 7.23 (1H, s, CH Thiazole) 7.61-8.02 (3H m, ArH), 9.76 (1H, bs, NH); Anal. calc. for $C_9H_8N_2S$: C, 41.08; H, 2.19; N, 8.71; S, 9.97; found C, 40.96; H, 2.06; N, 8.41; S, 9.86.

Results and Discussion

Figure 1 shows the reaction between aryl amine and chloroacetyl chloride to give N-substituted acetamides. The optimization of reaction conditions is given in table 1 and figure 2. To check the versatility of the reactions, wide range of substrate have been used and results are summarized in table 2. The result shows that the combination of DBU and THF gave the best result.

Figure 1.Reaction of aryl amine with chloroacetyl chloride in the presence of DBU

DBU (1,8-Diazabicyclo-[5.4.0]undec-7-ene) is commercially available, cheap homogenous catalyst. It is a sterically hindered bicyclic amidine base and especially useful where side reactions due to nucleophilicity of basic nitrogen are a problem.[19-21] DBU is one of the strongest organic neutral base (pKa = 12), in which the +M effect of the adjacent nitrogen stabilizes the protonated species, and it has been used in many organic reactions including amide bond formations in recent years.[22]

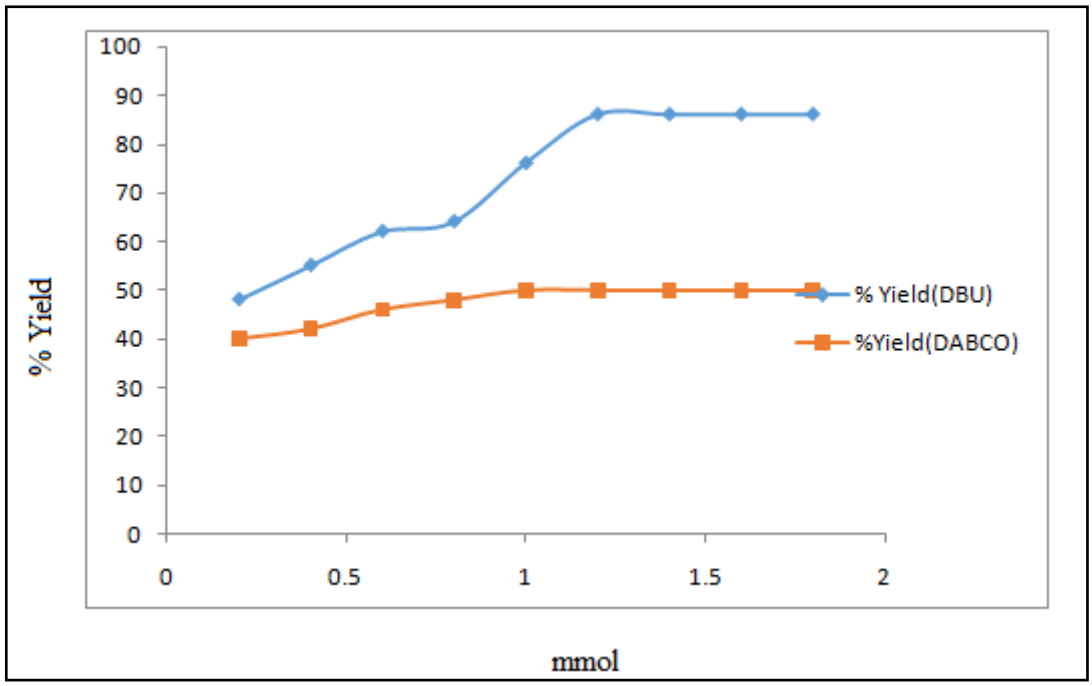


Figure 2. Comparative % yield optimization with DBU & DABCO for aniline (6 mmol)

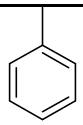
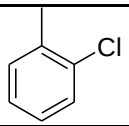
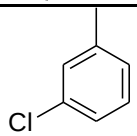
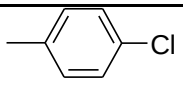
The reaction of aniline and chloroacetyl chloride was carried out in the presence of catalytic amount of DBU (Figure 1). We were pleased to observe that use of 1.2 mmol of DBU for 6 mmol of aryl amine significantly increases the rate of reaction and yield of the product at room temperatures (Figure 2). A wide

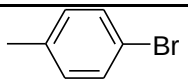
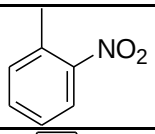
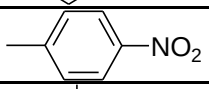
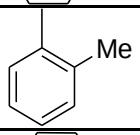
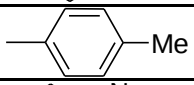
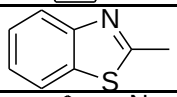
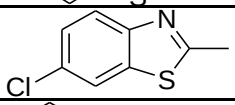
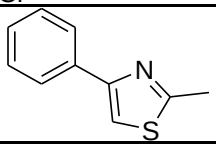
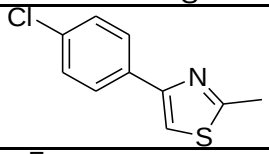
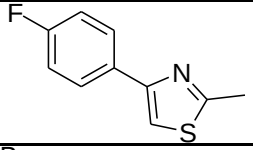
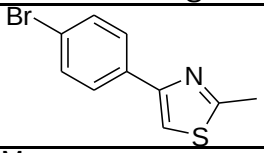
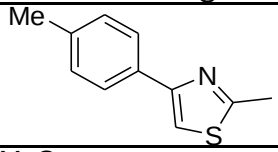
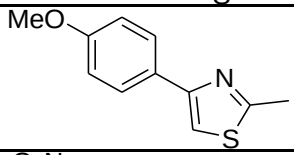
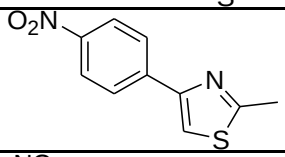
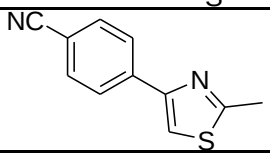
range of aryl amines such as aniline, 2-aminobenzothiazole, and 2-amino-4-phenylthiazole underwent one-pot reaction to produce the corresponding amides in 75-95% isolated yield. All the utilized functionalities were found to be compatible under the given reaction conditions. In a typical reaction, aniline (6 mmol) was dissolved in THF (5 ml) and then DBU (1.2 mmol) was added. The reaction mixture was placed on the freezing mixture of ice and salt & mechanically stirred for 15 min. Further, the chloroacetyl chloride (6.1 mmol) was added from dropping funnel at such rate that the temperature does not rise beyond 5^{o}C. The reaction mixture was further stirred at room temperature for 3 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was poured into cold water. The compound was precipitated out which was filtered and washed with water. The precipitate was dried and recrystallized using ethanol. The product, N-phenylacetamide (**1**) was obtained as a solid powder in 86% yield (Table 1 & 2). The same procedure was also followed for the substrates 2-aminobenzothiazole (entries 2, 5, 8, 11 & 14) and 2-amino-4-phenylthiazole (entries 3, 6, 9, 12 & 15) to check the versatility of the process. The optimization of catalysts DBU and DABCO (1,4-diazobicyclo(2,2,2)-octane) has been done for aniline in the different solvent system, and the same ratio applied to all other substrates under optimized reaction conditions (Figure 2). Out of many reactions, the ratio of 1:5 (DBU: aniline) in THF gave the best result (Table 1).

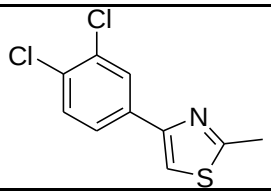
Table 1.Optimization of catalysts and solvents for compounds 1, 10&12.

Entry	Compd. No.	Solvent	% yield by using catalyst		
			DBU	DABCO	Et_3N
1	**1**	THF	86	68	70
2	**10**	THF	83	60	62
3	**12**	THF	86	63	64
4	**1**	1,4 dioxane	75	70	68
5	**10**	1,4 dioxane	71	64	69
6	**12**	1,4 dioxane	74	66	68
7	**1**	Benzene	58	50	56
8	**10**	Benzene	52	No reaction	50
9	**12**	Benzene	51	No reaction	51
10	**1**	DCM	72	62	65
11	**10**	DCM	70	58	61
12	**12**	DCM	70	59	64
13	**1**	DMF	74	74	69
14	**10**	DMF	71	69	64
15	**12**	DMF	73	68	65

Table 2.Amidation of chloroacetyl chloride with different aryl amines

Comp. No.	R	Time(h)	% Yield DBU	Mp (^{o}C)	Lit mp[ref]
1		3	86	136	134[24]
2		3	82	69-70	73[24]
3		3	80	100	98-100[12]
4		3	85	176	178[24]

5		3	85	182	180-184[12]
6		5	76	98	96-98[11]
7		5	79	180	178-180[11]
8		4	86	98-100	105-107[24]
9		4	88	164	164-166[24]
10		6	83	145	-
11		6	76	213	-
12		4	86	181	-
13		5	85	188-189	-
14		5	85	134-136	-
15		5	86	206	-
16		4	90	149	-
17		4	95	234	-
18		6	75	295-297	-
19		6	76	276-278	-

20		6	79	230	-

The reactions in the bases like TEA (triethylamine) and DABCO remained non-completed even after performing the reaction for the longer time. The reactant, aryl amines in both the cases was not consumed completely even after stirring for 10 hours at room temperature as observed in TLC. Hence, the products were separated by using column chromatography leading to low yield in comparison to DBU. The summary of comparative studies for different bases in the different solvent is given in table 1. The comparison of % isolated yield in case of DABCO and DBU for 6 mmol of aniline is in figure 1.

According to the proposed mechanisms, DBU provides significant acceleration compared to other amine bases. This suggests that DBU is not only acting as a base rather playing another role also. There are different pathways postulated to explain the role of DBU in these types of reactions.[23] According to our observation, the most suitable catalytic mechanism is the displacement of chloride ion by DBU and hence activates the carbonyl for attack by the lone pair of nitrogen present on aryl amines (Figure 3). However, further work to understand the pathways of the reaction is ongoing.

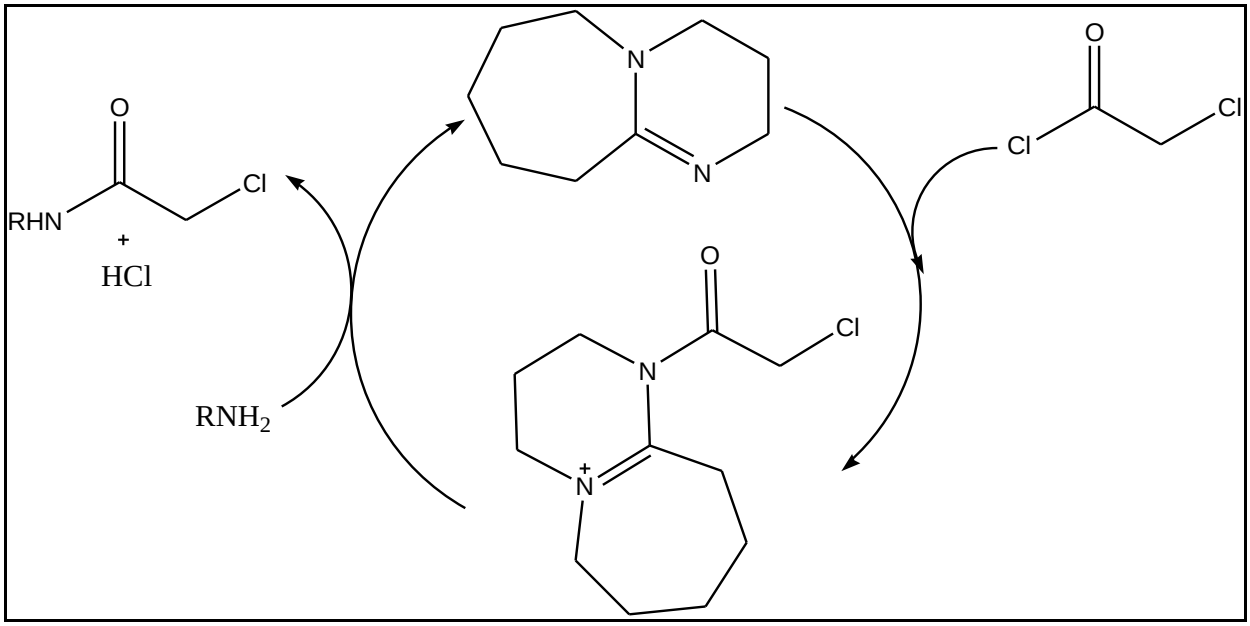


Figure 3.Proposed catalytic cycle

Conclusion

In present work, we have developed a facile method for the one-pot synthesis of amides from aryl amines and chloroacetyl chloride using DBU as non-nucleophilic base in THF solvent. The method gave 75 to 95% yields in 3-6 h at room temperature (rt). The reactions have also been performed in TEA and DABCO using different solvent system. The combination of DBU and THF gave best result. This method ensures the wide substrate scope with excellent yields and the products were isolated and purified by recrystallization.

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