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Direct Oxidative Amidation of Aldehydes with Anilines under Mechanical Milling Conditions

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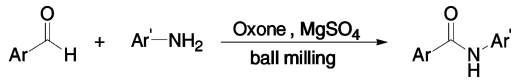


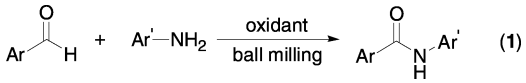
Oxone is found to be an effective oxidant for the oxidative amidation of aldehydes with anilines to furnish amides in a one-pot process under mechanical milling conditions.

The amide functional group is of importance in view of synthetic and biological aspects. Traditional synthetic methods for amides are mostly based on activated acid derivatives and amines. However, there are some limitations, including the lability of activated carboxylic acid derivatives and tedious procedures.

To circumvent these problems, alternative strategies toward the synthesis of amides have been explored for years. Due to the advanced properties, the use of transition-metal catalysts has developed rapidly in organic synthesis, and was also employed to promote the formation of amides. For example, transition-metal catalyzed amidations of nitriles,[1] aldehydes,[2] aldoximes,[3] alcohols,[4] alkenes,[5] alkynes,[6] and haloarenes[7] with amines have been reported. Although significant achievements were made, the relatively expensive transition metals greatly restricted the application of this methodology. Another notable access to the amide moiety was through the reactions of organic azides with terminal alkynes,[8] or thio acids,[9] which exhibited new promising routes for amide synthesis. Recently, the oxidative transformation of aldehydes[10] or arylalkynes[11] to amides has received much attention. Gunanathan et al. reported a successful example, in which the formation of amides was achieved by the direct oxidation of alcohols and amines.[12] However, most of these systems involved toxic solvents and transition-metal catalysts. Thus, developing new procedures for the synthesis of amides in both economic and eco-friendly ways is highly desirable. Recently, Wolf and co-worker presented an elegant alternative approach to amides without metal catalyst.[13]

Solvent-free organic reactions have drawn the attention of the chemical community for many years due to the public's increasing concern about environmentally benign processes. Our contribution to solvent-free reactions was focused on those promoted by the ball-milling technique.[14] In light of our recent success in this field,[15] we are interested in the direct oxidative amidations of aldehydes with amines under mechanical milling conditions.

Oxone (potassium peroxymonosulfate, $2KHSO_5{\cdot}KHSO_4{\cdot}K_2SO_4$), an efficient oxidant, found its broad applications in organic synthesis recently due to its versatility, stability, the simple handling, the nontoxic nature, and low costs.[16] Because of its prominent properties, we were intrigued to explore the feasibility of Oxone-promoted oxidative amidation. Herein, we report an efficient oxidative amidation process with Oxone under mechanical milling conditions (eq 1).



In our initial study, we chose the reaction of 3-nitrobenzaldehyde with *p*-toluidine and Oxone as the model reaction. Typically, a mixture of 3-nitrobenzaldehyde (0.1 mmol), *p*-toluidine (0.1 mmol), and Oxone (0.2 mmol) was milled vigorously at a rate of 1800 revolutions per minute (30 Hz) at room temperature for 90 min.[15b] After usual workup, the

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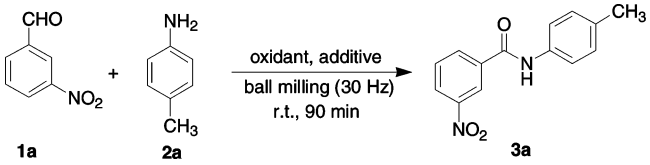
TABLE 1. Oxidative Amidation of 3-Nitrobenzaldehyde with *p*-Toluidine under Various Conditions[a]



1a 2a 3a

entry	oxidant	additives	solvent	yield[b] (%)
1	Oxone			61
2	Oxone	4Å MS		68
3	Oxone	$MgSO_4$		75
4	Oxone	$MgSO_4$	CH_3CN[c]	11
5	Oxone	$MgSO_4$	toluene[c]	trace
6	I_2	$MgSO_4$		0
7	$K_2S_2O_8$	$MgSO_4/ZnCl_2$		0
8	$K_2S_2O_8$	$MgSO_4$/CuCl		trace
9	$K_2S_2O_8$	$MgSO_4$/CuBr		0
10	$K_2S_2O_8$	$MgSO_4$/TsOH		0
11	$K_2S_2O_8$	$MgSO_4/KHSO_4$		0

[a] 3-Nitrobenzaldehyde (1.0 equiv), *p*-toluidine (1.0 equiv), $MgSO_4$ (1.0 equiv), and Oxone (2.0 equiv) in MM200 ball-mill. [b] Isolated yields. [c] 3-Nitrobenzaldehyde (1.0 equiv), *p*-toluidine (1.0 equiv), $MgSO_4$ (1.0 equiv), and Oxone (2.0 equiv) in solvent.

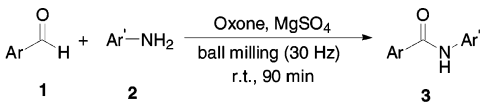
obtained product turned out to be the corresponding amide **3a**, i.e., 3-nitro-*N*-*p*-tolylbenzamide, yet in moderate yield of 61% along with various unidentified byproducts (entry 1, Table 1). We envisioned that the reaction might proceed through an imine intermediate; the thus generated water was harmful to the reaction. Molecular sieves (4 Å) were therefore added to remove the formed water. As desired, the product yield was improved slightly (entry 2, Table 1). Anhydrous magnesium sulfate was then examined. Much to our delight, the amidation reaction occurred more efficiently and cleanly to afford the product in 75% yield (entry 3, Table 1). When the imine generated from 3-nitrobenzaldehyde with *p*-toluidine was utilized as the starting substrate to react with Oxone, the same amide **3a** was obtained in 77% yield, which was slightly higher than the one-pot process.

To demonstrate the advantages of our solvent-free process, we further studied the oxidative amidation in organic solvents, including acetonitrile and toluene. As a result, the corresponding amide was obtained in rather low yields (entries 4 and 5, Table 1). Other oxidants including $K_2S_2O_8$ and I_2, were also examined. However, no reaction was observed (entries 6−11, Table 1). Oxone proved to be the most effective oxidant for this reaction. When the oxidant loading was reduced to 1.0 equiv, the yield decreased significantly. Hence 2.0 equiv of Oxone were necessary for this reaction.

With the optimized conditions in hand, we next investigated the scope and generality of this transformation with various aromatic aldehydes and anilines. The results are shown in Table 2. Although aryl aldehydes were prone to be oxidized to acids, only trace acids were observed in our procedure, which revealed that Oxone reacted chemoselectively with the imines rather than the aldehydes.

Anilines substituted with either electron-donating or electron-withdrawing groups, including *p*-toluidine, *p*-bromoaniline, and *p*-chloroaniline, exhibited similar activities (entries 1−11, Table 2). When aldehydes bearing electron-withdrawing groups were examined, the corresponding amides were obtained in moderate to good yields (entries 1−10, Table 2). The steric hindrance of the substituted groups on the phenyl rings of

TABLE 2. Direct Oxidative Amidation of Aldehydes with Anilines Using Oxone as the Oxidant under Solvent-Free Conditions[a]

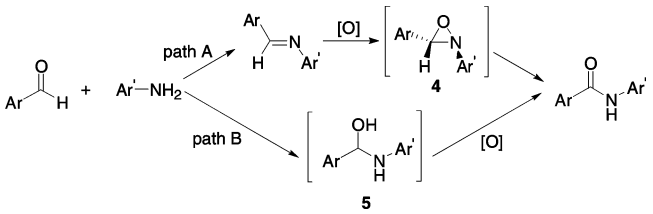


1 2 3

entry	Ar	Ar'	product	yield (%)[b]
1	3-NO_2-C_6H_4	4-CH_3-C_6H_4	**3a**	75
2	4-NO_2-C_6H_4	4-CH_3-C_6H_4	**3b**	78
3	4-CN-C_6H_4	4-CH_3-C_6H_4	**3c**	65
4	2-NO_2-C_6H_4	4-CH_3-C_6H_4	**3d**	38
5	3-NO_2-C_6H_4	4-Br-C_6H_4	**3e**	71
6	4-NO_2-C_6H_4	4-Br-C_6H_4	**3f**	66
7	4-CN-C_6H_4	4-Br-C_6H_4	**3g**	60
8	3,4-Cl_2-C_6H_3	4-Br-C_6H_4	**3h**	65
9	2-NO_2-C_6H_4	4-Br-C_6H_4	**3i**	45
10	3-NO_2-C_6H_4	4-Cl-C_6H_4	**3j**	62
11		4-CH_3-C_6H_4	**3k**	42

[a] Aldehyde (1.0 equiv), aniline (1.0 equiv), $MgSO_4$ (1.0 equiv), Oxone (2.0 equiv) in MM200 ball-mill. [b] Isolated yields obtained by chromatography on silica gel.

SCHEME 1. Possible Pathway for the Direct Oxidative Amidation of Aldehydes with Anilines



aldehydes was deleterious to the reaction, leading to decreased yields. For example, 2-nitrobenzaldehyde afforded the desired amides in remarkably decreased yields (entries 4 and 9 vs entries 1 and 5, Table 2). A heterocyclic aldehyde, namely 2-thiophenecarboxaldehyde, was also investigated. Under the same conditions, the desired product, *N*-(4-methylphenyl)thiophene-2-carboxamide, was obtained in 42% yield (entry 11, Table 2). Extending our procedure to aryl aldehydes with electron-donating groups and aliphatic aldehydes was unworkable, probably due to the electronic factors. These results indicated that the reaction was sensitive to the electronic character of aldehydes.

It is noteworthy that replacing the aldehydes with corresponding carboxylic acids did not afford the desired amides. Therefore, the possibility of oxidation of aldehydes to carboxylic acids by Oxone, followed by reaction with anilines to give amides should be excluded. Although the exact process of this transformation is unclear at the present stage, we still attempted to propose a tentative mechanism for the amidation reaction of aldehydes with anilines based on the above results and the known examples (Scheme 1). We envisioned that this direct oxidative amidation reaction may proceed by two pathways. In pathway A, imines were formed from aldehydes and anilines rapidly, which were oxidized by Oxone to generate oxaziridines **4** as the key intermediates. Rearrangement of oxaziridines to amides is known for both photochemical and thermal reactions.[17] The initial cleavage of the N−O bond followed by migration of the substituent (hydrogen) trans to the nitrogen lone pair results in the formation of amides **3**. In pathway B, carbinolamine intermediates **5** were generated after the nucleophilic

addition of anilines to aldehydes, and then were oxidized by Oxone to form the desired amide products. Even though control experiments showed that imines could be employed as the starting substrates to perform the amidation reaction to generate the amide products directly, the exact mechanism of this reaction remains obscure and both pathways could be operational.

In conclusion, we have demonstrated a simple and novel one-pot protocol to oxidize aryl aldehydes and anilines directly to amides in synthetic useful yields under mechanical milling conditions for the first time. Compared with the traditional liquid-phase reaction, this novel solvent-free and metal catalyst-free procedure makes the synthesis of amides more efficient, low cost, and ecofriendly. To the best of our knowledge, this is unprecedented. Further investigations in this direction are in progress.

Experimental Section

General Procedure for the Oxidative Amidation of Aldehydes and Anilines Leading to Amides. A mixture of aryl aldehyde (1.0 equiv), aniline (1.0 equiv), $MgSO_4$ (1.0 equiv), and Oxone (2.0 equiv) was introduced, together with a stainless ball of 7.0 mm diameter, into a stainless steel jar (5 mL). The same mixture was also introduced into a second parallel jar. The two reaction vessels were closed and fixed on the vibration arms of a ball-milling apparatus (Retsch MM200 mixer mill, Retsch GmbH, Haan, Germany) and were vibrated vigorously at a rate of 1800 revolutions per minute (30 Hz) at room temperature for 90 min. After completion of reaction, the reaction mixture was collected and dissolved in ethyl acetate. The solution was then evaporated to dryness and the resulting solid was purified by column chromatography on silica gel using ethyl acetate/petroleum ether as the eluent.

3-Nitro-*N*-*p*-tolyl-benzamide (3a): mp 158−159 °C (lit.[18] mp 159−161 °C); IR (KBr) cm^{-1} 3300, 1647, 1597, 1526, 1405, 1347, 1326, 1266, 814, 710, 514; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.68 (s, 1 H), 8.39 (d, J = 8.1 Hz, 1 H), 8.25 (d, J = 7.5 Hz, 1 H), 7.92 (bs, 1 H), 7.69 (t, J = 8.0 Hz, 1 H), 7.52 (d, J = 8.1 Hz, 2 H), 7.19 (d, J = 8.1 Hz, 2 H), 2.35 (s, 3 H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 163.0, 147.8, 136.3, 136.1, 134.1, 133.2, 130.1, 129.1, 126.0, 122.4, 120.5, 20.5; HRMS calcd for $C_{14}H_{12}N_2O_3$ m/z 256.0848, found m/z 256.0850.

4-Nitro-*N*-*p*-tolylbenzamide (3b): mp 201−203 °C (lit.[19] mp 203.5−204 °C); ^1H NMR ($CDCl_3$, 300 MHz) δ 8.32 (d, J = 8.1 Hz, 2 H), 8.03 (d, J = 8.1 Hz, 2 H), 7.84 (bs, 1 H), 7.51 (d, J = 8.1 Hz, 2 H), 7.20 (d, J = 8.1 Hz, 2 H), 2.36 (s, 3 H). This is a known compound, and the spectral data are identical to those reported in the literature.[20]

4-Cyano-*N*-*p*-tolylbenzamide (3c): mp 177−179 °C; IR (KBr) cm^{-1} 3346, 2233, 1654, 1597, 1525, 1406, 1322, 1297, 1259, 814, 760, 630, 505; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.96 (d, J = 8.1 Hz, 2 H), 7.79 (bs, 1H), 7.78 (d, J = 8.1 Hz, 2 H), 7.50 (d, J = 8.1 Hz, 2 H), 7.19 (d, J = 8.1 Hz, 2 H), 2.35 (s, 3 H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 163.9, 139.0, 136.2, 133.1, 132.4, 129.1, 128.5, 120.5, 118.3, 113.8, 20.5; HRMS calcd for $C_{15}H_{12}N_2O$ m/z 236.0950, found m/z 236.0954.

2-Nitro-*N*-*p*-tolylbenzamide (3d): mp 146−147 °C (lit.[18] mp 146−148 °C); IR (KBr) cm^{-1} 3275, 1649, 1598, 1526, 1405, 1355, 1323, 1265, 908, 812, 786, 708, 511; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.10 (d, J = 8.0 Hz, 1 H), 7.74−7.69 (m, 1 H), 7.64−7.58 (m, 2 H), 7.50 (bs, 1 H), 7.46 (d, J = 8.1 Hz, 2 H), 7.17 (d, J = 8.1 Hz, 2 H), 2.35 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.6, 146.3, 134.9, 134.8, 133.9, 132.9, 130.6, 129.6, 128.7, 124.6, 120.8, 21.0; HRMS calcd for $C_{14}H_{12}N_2O_3$ m/z 256.0848, found m/z 256.0843.

***N*-(4-Bromophenyl)-3-nitrobenzamide (3e):** mp 179−180 °C; ^1H NMR (DMSO-d_6, 300 MHz) δ 10.69 (s, 1 H), 8.78 (s, 1 H), 8.45 (d, J = 8.4 Hz, 1 H), 8.40 (d, J = 7.5 Hz, 1 H), 7.85 (t, J = 8.0 Hz, 1 H), 7.77 (d, J = 8.6 Hz, 2 H), 7.58 (d, J = 8.6 Hz, 2 H). This is a known compound, and the spectral data are identical to those reported in the literature.[21]

***N*-(4-Bromophenyl)-4-nitrobenzamide (3f):** mp 238−240 °C (lit.[22] mp 240 °C); ^1H NMR (DMSO-d_6, 300 MHz) δ 10.67 (s, 1H), 8.38 (d, J = 8.7 Hz, 2 H), 8.18 (d, J = 8.7 Hz, 2 H), 7.77 (d, J = 8.8 Hz, 2 H), 7.57 (d, J = 8.8 Hz, 2 H). This is a known compound, and the spectral data are identical to those reported in the literature.[23]

***N*-(4-Bromophenyl)-4-cyanobenzamide (3g):** mp 205−206 °C; IR (KBr) cm^{-1} 3354, 2225, 1674, 1591, 1524, 1488, 1393, 1312, 1290, 1239, 1068, 1004, 858, 829, 762, 655, 507; ^1H NMR (DMSO-d_6, 300 MHz) δ 10.59 (s, 1 H), 8.10 (d, J = 8.1 Hz, 2 H), 8.03 (d, J = 8.1 Hz, 2 H), 7.76 (d, J = 8.7 Hz, 2 H), 7.56 (d, J = 8.7 Hz, 2 H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 164.3, 138.7, 138.1, 132.5, 131.5, 128.6, 122.4, 118.3, 115.9, 114.0; HRMS calcd for $C_{14}H_9N_2O^{79}Br$ m/z 299.9898, found m/z 299.9900.

***N*-(4-Bromophenyl)-3,4-dichlorobenzamide (3h):** mp 158−160 °C; IR (KBr) cm^{-1} 3303, 1652, 1591, 1522, 1490, 1393, 1312, 1240, 1137, 1073, 1032, 1011, 822, 768, 668, 503; ^1H NMR (DMSO-d_6, 300 MHz) δ 10.49 (s, 1 H), 8.21 (s, 1 H), 7.94 (d, J = 8.5 Hz, 1 H), 7.82 (d, J = 8.5 Hz, 1 H), 7.75 (d, J = 8.7 Hz, 2 H), 7.56 (d, J = 8.7 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 163.9, 136.7, 136.6, 134.4, 133.4, 132.2, 130.9, 129.4, 126.4, 122.3, 118.0; HRMS calcd for $C_{13}H_8NO^{35}Cl_2{}^{79}Br$ m/z 342.9166, found m/z 342.9159.

***N*-(4-Bromophenyl)-2-nitrobenzamide (3i):** mp 200−202 °C; IR (KBr) cm^{-1} 3284, 1652, 1592, 1522, 1489, 1392, 1353, 1312, 1068, 1009, 820, 709, 505; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.13 (d, J = 8.0 Hz, 1 H), 7.74 (t, J = 7.4 Hz, 1 H), 7.67−7.62 (m, 2 H), 7.48 (s, 4 H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 164.2, 146.4, 138.2, 134.1, 132.4, 131.6, 131.0, 129.2, 128.9, 124.2, 121.6, 115.6; HRMS calcd for $C_{13}H_9N_2O_3{}^{79}Br$ m/z 319.9797, found m/z 319.9795.

***N*-(4-Chlorophenyl)-3-nitrobenzamide (3j):** mp 174−176 °C; IR (KBr) cm^{-1} 3303, 1656, 1596, 1525, 1494, 1400, 1348, 1323, 1091, 826, 717, 514; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.69 (s, 1 H), 8.42 (d, J = 8.0 Hz, 1 H), 8.26 (d, J = 7.5 Hz, 1 H), 7.94 (s, 1 H), 7.72 (t, J = 8.0 Hz, 1 H), 7.62 (d, J = 8.6 Hz, 2 H), 7.37 (d, J = 8.6 Hz, 2 H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 163.3, 147.7, 137.6, 136.0, 134.1, 130.1, 128.5, 127.8, 126.2, 122.4, 122.0; HRMS calcd for $C_{13}H_9N_2O_3{}^{35}Cl$ m/z 276.0302, found m/z 276.0303.

***N*-(4-Methylphenyl)thiophene-2-carboxamide (3k):** mp 162−164 °C (lit.[24] mp 163 °C); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.64 (s, 1 H), 7.62 (d, J = 3.7 Hz, 1 H), 7.54 (d, J = 4.9 Hz, 1 H), 7.49 (d, J = 8.3 Hz, 2 H), 7.17 (d, J = 8.3 Hz, 2 H), 7.14−7.11 (m, 1 H),

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2.34 (s, 3 H). This is a known compound, and the spectral data are identical to those reported in the literature.[25]

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Supporting Information Available: ^{1}H NMR spectra of **3a**−**k** and ^{13}C NMR spectra of **3a**,**c**,**d**,**g**−**j**. This material is available free of charge via the Internet at http://pubs.acs.org.

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