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PAPER

Facile access to amides and hydroxamic acids directly from nitroarenes

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A new method for synthesis of amides and hydroxamic acids from nitroarenes and aldehydes is described. The MnO_2 catalyzed thermal deoxygenation of nitrobenzene resulted in formation of reactive nitroso intermediate which on reaction with aldehydes provided amides and hydroxamic acids. The thermal neat reaction in presence of 0.01 mmol KOH predominantly led to formation of the hydroxamic acid whereas reaction in the presence of 1 mmol acetic acid produced amides as the only product.

Introduction

Amide bond constitutes fundamental functional unit of biochemistry and is the most common C-N bond present in proteins, synthetic polymers, natural products, pharmaceutical drugs, agrochemicals, perfumes, flavors and many industrial products.[1] Therefore the synthesis of the amide bond continues to be important in organic chemistry.[2] A number of elegant and commercially viable methods have been discovered,[3] including the most widely used acylation of amines by the activated carboxylic acids.[3b, 4] In addition, several new methods have been reported over the time including: (a) aminocarbonylation of aryl halides,[5] (b) transition-metal mediated coupling of amines and alcohols through dehydrogenation,[6] and oxime rearrangement,[7] (c) *N*-heterocyclic carbene mediated activation of aldehyde[8] and α-hydroxyenones;[9] (d) aldehyde oxidation using metal catalysts[3c, 10] such as Pd,[11] Cu,[12] Ru,[13] and lanthanide;[14] and (e) amidation using acyl surrogate from nitrile,[15] alkene,[16] thioacid or thioester,[17] alkyne,[18] acyl and aminyl radicals.[19] Other than this, the amidation has been reported through Mn catalyzed C-C bond cleavage,[20] and Staudinger reaction.[21] The nitro[22] and nitroso[23] groups have also been utilized as nitrogen source for amide synthesis.[23-24] Recently MnO_2 catalyzed amide bond formation from nitriles has been reported.[25]

In the present article, we report a MnO_2 catalyzed amide bond formation directly from aldehydes and nitroarenes (Figure 1). Our protocol could also be optimized for synthesis of N-hydroxamic acids, which are pharmacologically important[26] and are considered as bioisosters of carboxylic acids.[27]

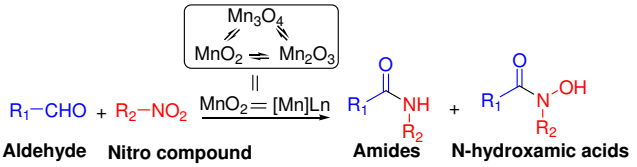

Figure 1 MnO_2-catalyzed amide bond formation.

Results and discussion

In one of our study on oxidation of a methyl group of chromone alkaloid rohitukine by in-situ generated nitroso intermediate from nitrobenzene, we observed the formation of hydroxamic acid and amide as byproducts (Section S1 of ESI). Exploring this reaction further, we discovered that nitrobenzene on reaction with benzaldehdye in presence of MnO_2 produce the corresponding amide and hydroxamic acid products in excellent yield. Considering the importance of this observation, we decided to explore the scope of this reaction in greater details.

The study was initiated with a preliminary reaction of 4-chlorobenzaldehyde **3a** with nitrobenzene **4a** in presence of 25 mol% MnO_2 under inert and neat medium for 48 h, which led to the formation of mixture of two products in 45% yield (Table 1, entry 3). Analysis by NMR and LCMS of product mixture confirmed these two products as amide **1a** and hydroxamic acid **2a** formed in the ratio of 50: 50 (Section S3a in ESI). The formation of hydoxamic acid **2a** indicated that reaction involved in-situ reduction of nitro to nitroso group.

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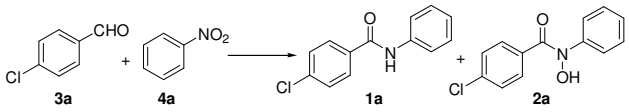
Table 1 Optimization of reaction conditions



Entry	Catal. (mol%)	Additive (mmol)	Solvent	Temp (°C)	Time (h)	Yield (%)[a] (**1a**+**2a**)	Ratio[b] of **1a**: **2a**
1	none	none	none	150	48	0	0
2	MnO_2 (25)	none	none	25	48	0	0
3	MnO_2 (25)	none	none	120	48	45	50: 50
4	MnO_2 (25)	none	$CHCl_3$[c]	60	48	10	nd
5	MnO_2 (25)	none	THF	70	48	20	nd
6	MnO_2 (25)	none	dioxane	100	48	20	nd
7	MnO_2 (25)	none	toluene	120	48	35	nd
8	MnO_2 (25)	none	xylene	120	48	35	nd
9	MnO_2 (10)	none	none	120	48	20	nd
10	MnO_2 (20)	none	none	120	48	30	nd
11	MnO_2 (30)	none	none	120	48	45	nd
12	MnO_2 (25)	KOH (0.01)	none	120	48	55	44: 56
13[d]	**MnO_2 (25)**[e]	**KOH (0.01)**	**none**	**120**	**48**	**70**	**30: 70**
14	MnO_2 (25)[f]	KOH (0.01)	THF	120	48	79	48: 52
15[d]	**MnO_2 (25)**	**AcOH (1)**	**$CHCl_3$**[g]	**60**	**12**	**90**	**100: 0**
16	MnO_2 (25)	AcOH (1)	CH_2Cl_2[g]	25	48	30	100: 0
17	MnO_2 (25)	AcOH (1)	MeOH[h]	60	50	20	100: 0

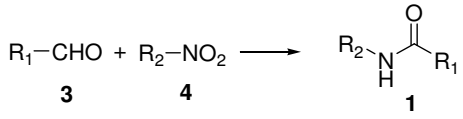
[a] The combined yield (**1a** + **2a**) is an isolated yield
[b] individual ratios of **1a** and **2a** were determined by LCMS (see, Section S3 of ESI).
[c] Similar results were observed with CH_2Cl_2 and CCl_4.
[d] the bold entry 13 indicates optimized reaction conditions for synthesis of hydroxamic acids; and bold entry 15 is optimized condition for synthesis of amides.
[e] catalyst added in portion-wise (3 batches).
[f] The **3a**, **4a**, MnO_2 and KOH were mixed in THF under sonication, followed by compete evaporation of solvent. Remaining residue was heated at 120 °C for 48 h.
[g] Similar results were observed when THF or dioxane were used.
[h] similar results were observed with EtOH.

Next, the optimization experiments (solvent and temperature) were carried out to improve the yield of the amide **1a** (Table 1) using the aldehyde **3a** and nitrobenzene **4a**. Under neat condition, product was not obtained at room temperature (entry 2); however 45% yield was obtained at 120 °C (entry 3). Then, we investigated effect of solvent in this reaction. It was noticed that solvent played an important role, as methanol, ethanol, DMF and DMSO were found to interfere with the reaction. However, when CH_2Cl_2, $CHCl_3$ and CCl_4 were used as solvents at their reflux temperatures, both the products (**1a** and **2a**) were formed albeit in poor yield (entry 4). The yields got marginally improved when high boiling point solvents (dioxane, toluene and xylene) were used (entries 6-8). The catalyst loading of 25 mol% was found to be suitable (entries 3 and 9-11). The reaction in closed airtight vessel either failed to give product or led to very poor yields, possibly due to the presence of gaseous side products (mainly H_2O and CO_2) in the reaction vessel which reduced the initial reduction of nitro to nitroso group, as explained in Mars-van Kravelen mechanism.[28] The KOH has been reported to enhance the conversion of nitro to nitroso.[29] The addition of KOH (0.01 mmol) to the reaction mixture, significantly promoted yield of the products (entry 12) with the ratio of **1a: 2a** as 44: 56. Moreover, we also observed that the sequence of the addition of the catalyst MnO_2 impacted the yield, as the addition of catalyst in portions was beneficial (entry 13 vs. 12), where the overall yield improved up to 70% and ratio of amide: hydroxamic acid changed to 30: 70. The reaction condition described in the entry 13 (without solvent) was found optimal (70%) for the synthesis of amide and hydroxamic acid, which were isolated in the ratio of 3:7. In the next set of experiments, the substrates **3a** and **4a**, catalyst (MnO_2) and additive (KOH) were all mixed in THF by sonication followed by the evaporation of solvent. The remaining residue when heated at 120 °C for 48 h led to 79% yield (entry 14) of the product mixture of amide and hydroxamate. Interestingly, in a further experiment, when the reaction was performed in $CHCl_3$ in presence of acetic acid (entry 15) at reflux temperature, the corresponding amide was obtained as the only product in 90% yield.

The scope of this reaction was then investigated using optimized reaction conditions (entry 15 of Table 1). The substitution of aldehydes with various groups was well tolerated (Table 2, entries 1-12). The heterocyclic aldehyde also participated well in this reaction (entry 9). In the case of nitroarenes, the reaction worked well with nitrobenzene as well as with heterocyclic nitrene (entry 12). All our attempts with aliphatic nitro compounds failed to get desirable amides, possibly due to the reactive nitroso getting stabilized through isomerization with available α-hydrogen of RCH_2NO to the corresponding oxime

RCH=NOH and thus restricting the desired reaction (entry 15). It was also observed that *O*-iodo-nitrobenzene (**4m**) and o-bromo-nitrobenzene (**4n**) failed to produce desired amide in practical yields (7-8%; Table 2), perhaps due to the formation of azodioxy dimer side product (Section S2 of ESI).

Table 2 Scope of the reaction[a]



Entry	R_1	R_2	Product	Yield[b]
1	-Ph (4-Cl)	-Ph	**1a**	90
2	-Ph	-Ph	**1b**	85
3	-Ph (2,6-di-Cl)	-Ph	**1c**	88
4	-Ph (2,4,5-tri-OMe)	-Ph	**1d**	79
5	-Ph (3-Br, 4-F)	-Ph	**1e**	76
6	-Ph (4-F)	-Ph	**1f**	86
7	-Ph (3,5-di-OMe)	-Ph	**1g**	85
8	-Ph (2-Cl)	-Ph	**1h**	76
9	5-Me-pyrazin-2-yl	-Ph	**1i**	78
10	-Ph (2-Me)	-Ph	**1j**	76
11	-Ph (3-OH, 4-OMe)	-Ph	**1k**	84
12	-Ph (2,4,5-OMe)	2-pyridinyl	**1l**	76
13	-Ph (3,4,5-OMe)	-Ph (2-I)	**1m**	7[c]
14	-Ph	-Ph (2-Br)	**1n**	8[c]
15	-Ph	1-propanyl	**1o**	0[d]

[a] Reagents and conditions (optimized condition, entry 15 from Table 1): aldehyde (**3**, 1 mmol), nitro compound (**4**, 1.2 mmol), MnO_2 (25 mol%), AcOH (1 mmol) in chloroform, refluxed at 60 °C for 12 h.

[b] isolated yield of amides.

[c] corresponding dimeric azodioxy was a major side product.

[d] corresponding oxime was isolated as major product.

We are investigating the mechanism of this important new reaction to prepare amides and hydroxamic acids, and will report in due course.

Conclusion

In summary, we have reported Mn-oxide catalyzed new method for synthesis of amides and hydroxamic acids from nitroarenes. The reaction opens up new opportunities to discover nitroarene-based methodologies for practical applications in medicinal and industrial chemistry for synthesis of amides and hydroxamic acids.

Experimental Section

General information. All chemicals were obtained from Sigma-Aldrich Company and used as received. The ^1H, and ^{13}C NMR spectra were recorded on Bruker-Avance DPX FT-NMR 500 and 400 MHz instruments. Chemical data for protons are reported in parts per million (ppm) downfield from tetramethylsilane and are referenced to the residual proton in the NMR solvent ($CDCl_3$, 7.26 ppm). Carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded at 125 or 100 MHz; chemical data for carbons are reported in parts per million (ppm, δ scale) downfield from tetramethylsilane and are referenced to the carbon resonance of the solvent ($CDCl_3$, 77 ppm). ESI-MS and HRMS spectra were recorded on Agilent 1100 LC-QTOF and HRMS-6540-UHD machines. LC-ESI-MS/MS analysis was carried out on Agilent Triple-Quad LC–MS/MS system (model 6410).

General method of synthesis of amides 1a-1n (Table 1, entry 15). To the mixture of MnO_2 (25 mol%, added in 3-portions), aldehyde (1 equiv.) and acetic acid (1 equiv.) was added nitrobenzene (1.2 equiv.) in chloroform and reaction mixture was heated at 60 °C for 12 hrs under nitrogen environment. Reaction was monitored by TLC and MS analysis. After completion of the reaction (usually 12 h), the reaction mixture was filtered, concentrated and partitioned in ethyl acetate and water. The organic layer was dried over anhydrous sodium sulphate and concentrated. Purification on silica gel column chromatography gave amides **1a-n** in 8-90% yield.

4-Chloro-N-phenylbenzamide (1a). Yield: 78%; white needles; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.84-7.81 (m, 2H), 7.75 (s, NH), 7.65 (d, J = 8.2 Hz, 2H), 7.63 (m, 2H), 7.48 (t, J = 7.2 Hz, 2H), 7.39 (t, J = 7.3 Hz, 2H), 7.18 (t, J = 7.2 Hz, 1H); ESIMS: *m/z* 232.0 $[M+H]^+$; HRMS: *m/z* 232.0511 $[M+H]^+$ calcd for $C_{13}H_{11}ClNO^+$ (232.0523).[24]

N-Phenylbenzamide (1b). Yield: 70%; white crystals; ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.89-7.87 (m, 2H), 7.19 (s, NH), 7.65 (d, J = 8.2 *Hz*, 2H), 7.56-7.48 (m, 5H), 7.39 (t, 2H, J = 8.0 Hz), 7.16 (t, 1H, J= 8Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): 168, 139.9, 136.3, 132.9, 129.8, 129.6, 128.6, 125.6, 122.3. ESIMS: *m/z* 198.0 $[M+H]^+$; HRMS: *m/z* 198.0921 $[M+H]^+$ calcd for $C_{13}H_{12}NO^+$ (198.0913).[24]

2,6-Dichloro-N-phenylbenzamide (1c). Yield: 71%; white needles; ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.65 (m, 2H), 7.48-7.26 (m, 6H), 7.22 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.4, 137.1, 135.9, 132.4, 130.9, 129.1, 128.1, 125.2, 120.3; ESIMS: *m/z* 266.0 $[M+H]^+$; HRMS: *m/z* 266.0121 $[M+H]^+$ calcd for $C_{13}H_{10}Cl_2NO^+$ (266.0134).[30]

2,4,5-Trimethoxy-N-phenylbenzamide (**1d**). Yield: 68%; crystalline solid; ^1HNMR ($CDCl_3$, 400 MHz): δ 9.85 (s, 1H), 7.83 (s, 1H), 7.67 (d, 2H, J = 8.0 *Hz*), 7.36 (t, 2H, J = 8.0 *Hz*), 7.12 (t, 1H, J = 8.0 *Hz*), 4.06 (s, 3H), 3.97 (s, 3H), 3.93 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 163, 153.4, 153.2, 143.7, 136.6, 128.9, 123.9, 120.9, 114.0, 113.5, 96.9, 57.1, 56.3, 56.2; ESIMS: *m/z* 288.1 $[M+H]^+$; HRMS: *m/z* 288.1221 $[M+H]^+$ calcd for $C_{16}H_{18}NO_4^+$ (288.1230).[31]

3-Bromo-4-fluoro-N-phenylbenzamide (**1e**). Yield: 76%; white solid; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.10 (d, 1H, J = 8.0 *Hz*), 7.82 (m, 1H), 7.71 (s, 1H), 7.62 (s, 2H, J = 8.0 *Hz*), 7.39 (t, 2H, J = 8.0 *Hz*), 7.20 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163, 159.9, 137.4, 132.4, 129.1, 128.1, 125.0, 120.3, 116.9, 109.8. 56.2; ESIMS: *m/z* 293.9 $[M+H]^+$; HRMS: *m/z* 293.9922 $[M+H]^+$ calcd for $C_{13}H_{10}BrFNO^+$ (293.9924).

4-Fluoro-N-phenylbenzamide (1f). Yield: 76%; white solid; ^1H NMR ($CDCl_3$, 400 MHz): δ 10.40 (s, 1H, NH), 8.04 (m, 2H, J = 8 Hz), 7.76 (d, 2H, J = 8 Hz), 7.36 (m, 4H), 7.11 (t, 1H, J = 8

Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 166.4, 164.5, 163.0, 137.3, 131.1, 129.4, 129.3, 129.1, 124.7, 120.2, 116.0, 115.8; ESIMS: *m/z* 216.2 [M+H] $^+$; HRMS: *m/z* 216.0822 $[M+H]^+$ calcd for $C_{13}H_{11}FNO^+$ (216.0819).[24]

3,5-Dimethoxy-N-phenylbenzamide (1g). Yield: 70%; white solid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.81 (s, 1H, NH), 7.65-7.61 (m, 3H), 7.41-7.35 (m, 3H), 6.94-6.88 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.0, 153.7, 148.7, 129. 0, 124.6, 124.4, 121.7, 120.1, 119.4, 112.3, 110.3, 56.0; ESIMS: *m/z* 258.1 $[M+H]^+$; HRMS: *m/z* 258.1111 $[M+H]^+$ calcd for $C_{15}H_{16}NO_3^+$ (258.1124).[32]

2-Chloro-N-phenylbenzamide (1h). Yield: 72%; white solid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.8 (s, NH), 7.77 (1H, dd, *J* = 4.0, 8.0 *Hz*), 7.66 (2H, dd, *J* = 4.0, 8.0 *Hz*), 7.47-7.38 (m, 5H), 7.18 (1H, t, *J* = 4.0 *Hz*); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.2, 139.6, 138.1, 132.2, 132.0, 131.0, 129.9, 128.2, 125.2, 121.5. ESIMS: *m/z* 232.6 $[M+H]^+$; HRMS*: m/z* 232.0511 $[M+H]^+$ calcd for $C_{13}H_{11}ClNO^+$ (232.0523).[33]

5-Methyl-N-phenylpyrazine-2-carboxamide (**1i**). Yield: 72%; white crystals; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.96 (s, 1H), 9.38 (s, 1H), 8.45 (s, 1H), 7.76 (d, 2H, *J* = 8.0 *Hz*), 7.40 (t, 2H, *J* = 8.0 *Hz*), 7.18 (t, 1H, *J* = 8.0 *Hz*); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 161.2, 157.2, 143.7, 142.0, 141.7, 137.4, 129.1, 124.6, 119.7, 21.9; ESIMS: *m/z* 214.0 $[M+H]^+$; HRMS: *m/z* 214.0951 $[M+H]^+$ calcd for $C_{12}H_{12}N_3O^+$ (214.0975).

2-Methyl-N-phenylbenzamide (**1j).** Yield: 55%; white crystals; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.68 (s, NH), 7.59 (d, *J*= 4.0 *Hz*, 2H), 7.37 (d, 1H, *J* = 4.0 Hz), 7.33 (t, *J* = 8.0 *Hz,* 3H), 7.24-7.11 (m, 3H), 2.5 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 168, 138, 136.4, 131.2, 130.2, 129.1, 126.6, 125.8, 124.5, 119.9, 19.8; ESIMS: *m/z* 212.2 $[M+H]^+$; HRMS: *m/z* 212.1039 calcd for $C_{14}H_{14}NO^+$ (212.1069).[24]

3-Hydroxy-4-methoxy-N-phenylbenzamide (**1k**). Yield: 71%; crystalline solid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.0 (s, 1H, OH), 9.30 (s, 1H, NH), 7.75 (d, *J* = 8.0 Hz, 2H), 7.46 (d, 1H, *J* = 12.0 Hz), 7.41 (s, 1H), 7.33 (t, *J* = 8.0 Hz, 2H), 7.05 (m, 2H), 3.85 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.2, 151.8, 150.9, 146.2, 145.9, 138.5, 128.3, 127.3, 127.0, 120.9, 119.5, 114.3, 110.4, 55.1; ESIMS: *m/z* 244.0 $[M+H]^+$; HRMS: *m/z* 244.0977 $[M+H]^+$ calcd for $C_{14}H_{14}NO_3^+$ (244.0968).

2,4,5-Trimethoxy-N-(pyridin-2-yl)benzamide (**1l**). Yield: 55%; white needles; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.82 (s, NH), 8.42 (1H, d, *J*= 4.0 Hz), 8.31 (m, 1H), 7.8 (m, 1H), 7.19-7.14 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 166.6, 153.2, 151.7, 139.3, 119.8, 114.9, 107.4, 60.9, 56.3; ESIMS: *m/z* 289.3 $[M+H]^+$; HRMS: *m/z* 289.1152 [M+H] $^+$ calcd for $C_{15}H_{17}N_2O_4^+$ (289.1182).

General method of synthesis of hydroxamic acids (Table 1, entry 13). To the mixture of MnO_2 (25 mol%, added in 3-portions), aldehyde (1 equiv.) and KOH (0.01 mmol; added in portion-wise in 3 batches) was added nitrobenzene (1.2 equiv.) and reaction mixture was heated at 120 °C under nitrogen atmosphere for 48 h. The purification using silica gel column chromatography gave amide and hydroxamic acid in 30: 70 ratio.

4-Chloro-N-hydroxy-N-phenylbenzamide (2a). White solid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.84 (d, *J* =12.0 Hz, 2H), 7.75 (s), 7.64 (d, *J* = 8.2 Hz, 2H), 7.50 (d, *J* =12.0 Hz, 2H), 7.40 (t, *J* = 8.0 Hz, 2H), 7.18 (t, *J* = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 150.51, 138.54, 137.40, 133.21, 129.17, 129.09, 128.40, 124.82, 120.21; ESIMS: *m/z* 248.3 $[M+H]^+$; HRMS: *m/z* 248.0462 $[M+H]^+$ calcd for $C_{13}H_{11}ClNO_2^+$ (248.0473).

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