Catalytic Amination of Aldehydes to Amides

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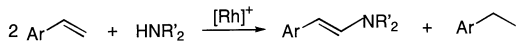
Aldehydes react in a disproportionation reaction in the presence of rhodium catalysts to yield amines and amides. By adding *N*-methylmorpholine *N*-oxide as an oxidant in the presence of catalytic amounts of rhodium, the oxidative amination of aldehydes proceeds selectively to give the corresponding amide. Both aliphatic and aromatic aldehydes react with secondary amines to yield carboxylic acid amides in good to excellent yields.

Introduction

Aromatic and aliphatic amides are of significant importance in organic chemistry as integral parts of polymers, natural products, and pharmaceuticals. In general, amides are synthesized from amines and activated carboxylic acid derivatives with the same oxidation level as the resulting product.[1] Another attractive method is the aminocarbonylation of olefins with carbon monoxide and amines in the presence of late transition metal catalysts.[2] An alternative approach, from economically attractive and available starting materials, is the direct oxidative amination of aldehydes. So far, only a few examples of this type of process have been reported. Among them the palladium- and ruthenium-catalyzed transformations of aldehydes to amides are the only transition metal-catalyzed variants known.[3] The palladium-catalyzed reaction, however, requires the use of a stoichiometric amount of aryl bromide as the oxidant, and the ruthenium-catalyzed reaction proceeds with only moderate yields. Similarly, oxidative amidations require the use of a stoichiometric or excess amount of transition metal.[4]

Recently, we have discovered new types of oxidative aminations of olefins with amines to give enamines (Scheme 1).[5]

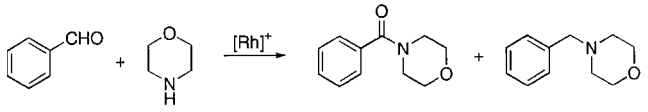


Scheme 1

The key factor for success in this reaction is the use of a cationic rhodium catalyst. Here we report for the first time a rhodium-catalyzed oxidative amination of aldehydes to give various aliphatic and aromatic amides in good to excellent yields.

Results and Discussion

In order to develop a new domino sequence consisting of oxidative amination of olefins and subsequent aldol reaction, we studied the reaction of benzaldehyde with styrene and morpholine in the presence of catalytic amounts of $[Rh(COD)_2]BF_4$ in THF at 100 °C. Surprisingly, we observed *N*-benzylmorpholine and *N*-benzoylmorpholine as major products, making it clear that styrene did not take part in this reaction. Therefore we investigated the reaction of benzaldehyde and morpholine (Scheme 2) more closely.



Scheme 2

N-benzoylmorpholine was obtained in 52% yield, from benzaldehyde (4.40 mmol), morpholine (2.20 mmol), $[Rh(COD)_2]BF_4$ (0.055 mmol), and PPh_3 (0.11 mmol). In addition 15% of *N*-benzylmorpholine and small amounts (< 2%) of benzyl alcohol and benzyl benzoate were isolated. This new type of disproportionation reaction requires the presence of a cationic rhodium catalyst. In the absence of rhodium or in the presence of $[Rh(COD)Cl]_2 \cdot 2PPh_3$, no amide formation was observed. Instead, the 2:1-addition product of morpholine and benzaldehyde $PhCH[N(CH_2CH_2)_2O]_2$ could be detected. Variation of the ratio of benzaldehyde to morpholine showed that the amide yield increased up to 65% with an increasing amount of benzaldehyde (Table 1, entries 1−3). Using toluene as the solvent similar reactions were observed, although *N*-benzylmorpholine and *N*-benzoylmorpholine were produced in equal amounts (Table 1, entries 4−6).

As shown in Table 1, other secondary amines (e.g. piperidine, *N*-methyl-*N*-butylamine) as well as other aliphatic and aromatic aldehydes (e.g. *o*-tolylaldehyde, *p*-fluorobenzaldehyde, *p*-methoxy-benzaldehyde, and cyclohexanecarbaldehyde) undergo similar disproportionation reactions albeit in lower yields. Primary amines such as aniline and *n*-butylamine give exclusively the corresponding imines.

With regards to the mechanism of the rhodium-catalyzed oxidative amination of aldehydes, we propose that the amine and aldehyde react to form the corresponding amino alcohol (Scheme 3). This amino alcohol may coordinate to the rhodium(I) complex. This coordination is preferred for cationic rhodium complexes rather than the formation of

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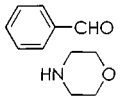
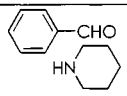
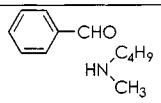
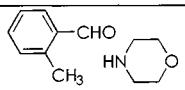
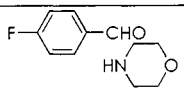
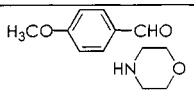
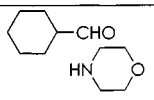
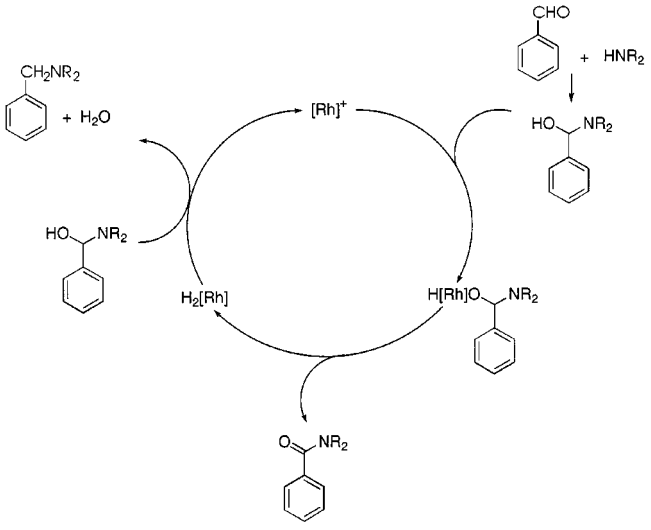
Table 1. Reaction of aldehydes with amines catalyzed by $[Rh(COD)_2]BF_4 \cdot 2PPh_3$ [a]

Entry	Reactants	Molar ratio aldehyde/amine	Solvent	Temp [°C]	Yield of amine [%][b]	Yield of amide [%][b]
1		1.2:1	THF	100	8	35
2		2:1	THF	100	15	52
3		3:1	THF	100	18	65
4		1:1	toluene	140	23	25
5		2:1	toluene	140	42	44
6		4:1	toluene	140	45	49
7		1:2	toluene	140	14	29
8		2:1	THF	100	4	16
9		3:1	THF	100	5	26
10		2:1	toluene	140	34	36
11		2:1	THF	100	10	30
12		3:1	THF	100	13	41
13		2:1	toluene	140	23	25
14		3:1	toluene	120	19	29
15		2:1	toluene	140	22	23
16		2:1	toluene	140	6	27
17		2:1	THF	100	5	29
18		2:1	toluene	140	38	28
19		2:1	THF	100	16	22
19		2:1	toluene	140	54	8

[a] General conditions: 4.40 mmol aldehyde, 2.20 mmol amine (or as described in the table), 0.055 mmol $[Rh(COD)_2]BF_4$ (2.5 mol-%), 0.11 mmol PPh_3, 20 h. – [b] The yield was determined by GC using an internal standard (hexadecane).

halide bridged complexes. Dehydrogenation of the amino alcohol yields the corresponding amide and a rhodium(III) dihydride complex, which reduces the aldehyde to the corresponding alcohol, or the aminal to the amine.



Scheme 3

This mechanism explains all of the observed products as well as the necessity to use cationic rhodium complexes. In order to make the oxidative amination of aldehydes more useful for synthetic applications, the reduction of aldehyde to alcohol, and side-reactions of the alcohol have to be avoided. We thought that the addition of *N*-methylmorpholine *N*-oxide would result in the regeneration of a catalytically active rhodium dehydrogenation catalyst. In addition, the use of a base as co-catalyst should increase the rate of the dehydrogenation step. Indeed, the reaction of benzaldehyde (4.40 mmol), morpholine (2.20 mmol), *N*-methylmorpholine *N*-oxide (2.20 mmol), $[Rh(COD)_2]BF_4$ (0.055 mmol), and potassium carbonate (0.22 mmol) in THF at 100 °C proceeds much more selectively: *N*-benzoylmorpholine is obtained in >99% yield! After some optimization work, piperidine and methyl-*n*-butylamine yielded *N*-benzoylpiperidine and *N*-benzoyl-*N*-methyl-*N*-*n*-butylamine in 96% and 94% respectively (Table 2, entries 11 and 17); primary amines, however, gave exclusively the corresponding imines (Table 2, entry 19).

In all of these reactions, only traces of benzylamines were detected. Catalytic amounts of potassium carbonate (0.1

Table 2. Reaction of benzaldehyde with different amines catalyzed by $[Rh(COD)_2]BF_4$ in the presence of *N*-methylmorpholine *N*-oxide/K_2CO_3 [a]

Entry	Amine	Molar ratio aldehyde/amine	Solvent	Temp. [°C]	Time [h]	Yield of amide [%][b]
1		2:1	toluene	140	8	100
2		2:1	THF	100	8	100
3		2:1	toluene	140	8	82[c]
4		1:2	toluene	140	8	100
5		1.2:1	toluene	140	8	88
6		2:1	toluene	140	8	78
7		2:1	toluene	140	8	78[d]
8		2:1	toluene	140	20	89
9		1:2	toluene	140	8	83
10		1:3	toluene	140	8	84
11		1:2	toluene	140	20	96
12		2:1	toluene	140	8	35
13		2:1	toluene	140	20	33
14		2:1	toluene	120	20	54
15		2:1	toluene	100	20	69
16		1:2	toluene	100	20	61
17		2:1	THF	100	20	94
18		1:2	THF	100	20	63
19	aniline	2:1	toluene	140	8	–

[a] General conditions: 4.40 mmol aldehyde, 2.20 mmol amine (or as described in the table), 0.055 mmol $[Rh(COD)_2]BF_4$ (2.5 mol-%), 2.20 mmol *N*-methylmorpholine *N*-oxide, 0.22 mmol K_2CO_3. – [b] The yield was determined by GC using an internal standard (hexadecane). – [c] 1 mol-% catalyst. – [d] 2.20 mmol K_2CO_3.

equiv.) are sufficient for an improved transformation of aldehydes to amides. Using a stoichiometric or excess amount of potassium carbonate did not increase the yield of the amide any further. In general an excess of the aldehyde is used in order to obtain the highest yields of amide, but in the case of piperidine an excess of amine is necessary to get optimum results with benzaldehyde.

In addition to benzaldehyde, *o*-tolylaldehyde and *p*-fluorobenzaldehyde were converted into amides with morpholine in excellent yields (94−100%, Table 3). Using *p*-fluorobenzaldehyde, nucleophilic aromatic substitution of the *p*-fluoro substituent was observed as a side-reaction. The yield of *N*-(4-fluorobenzoyl)morpholine was mainly influenced by the reaction temperature. The highest yields were realized at 100 °C in THF. In toluene at higher temperatures, a considerable amount of 4-morpholinobenzaldehyde was formed.

Under standard conditions the less activated *p*-methoxybenzaldehyde provided only moderate yields of the amide. Remarkably, an excess of morpholine did not give the expected aminal, but a higher yield of the amide. Cyclohexanecarbaldehyde also provided a better yield of the amide if an excess of morpholine was used. The best yields of amide are obtained at 100 °C in THF. Otherwise, significant amounts of the *N*-(cyclohexylmethyl)morpholine were produced.

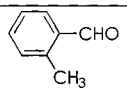
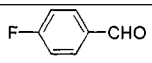
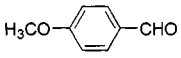
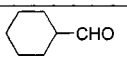
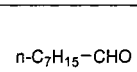
All attempts to react *n*-octanal with morpholine gave α-octylidenomorpholine and octanoylmorpholine. Satisfactory yields of the desired amide were obtained by using an excess of morpholine.

In conclusion, we have developed a new rhodium-catalyzed oxidative amination of aldehydes. By variation of the amine/aldehyde ratio, good to excellent yields of dialkylamides are obtained. The new method makes use of ubiquitously available starting materials and is the most efficient procedure to synthesize amides from aldehydes known to date.

Experimental Section

General: All operations were carried out under an inert atmosphere of argon. Toluene and THF were freshly distilled from sodium tetraethylaluminate under argon prior to use. Amines were distilled from CaH_2. Aldehydes were dried over 4 Å molecular sieves and distilled before use. Triphenylphosphane, *N*-methylmorpholine *N*-oxide, and potassium carbonate were purchased from Aldrich.

Table 3. Reactions of different aldehydes with morpholine catalyzed by $[Rh(COD)_2]BF_4$ in the presence of *N*-methylmorpholine *N*-oxide/K_2CO_3 [a]

Entry	Aldehyde	Molar ratio aldehyde/amine	Solvent	Temp [°C]	Time [h]	Yield of amine [%][b]	Yield of Amide [%][b]
1		2:1	toluene	140	8		100
2		1:2	toluene	140	8	-	82
4		2:1	THF	100	8	-	80
5		2:1	THF	100	20	-	94
6		1:2	THF	100	8	-	56
7		2:1	toluene	140	8	-	57
8		3:1	toluene	140	8	-	63
9		1:2	toluene	140	8	-	67
10		1:2	toluene	140	20	-	62
11		1:3	toluene	140	8	-	84
12		2:1	toluene	140	8	52	40
13		1:2	toluene	140	8	19	60
14		2:1	THF	100	8	40	48
15		1:2	THF	100	8	3	58
15		2:1	toluene	140	8	-	29
16		1:2	toluene	140	8	-	56
17		1:2	toluene	140	20	-	59
18		1:3	toluene	140	8	-	61

[a] All reactions were carried out with 4.40 mmol aldehyde, 2.20 mmol amine (or as described in the Table), 2.20 mmol *N*-methylmorpholine *N*-oxide, 0.22 mmol potassium carbonate, and 2.5 mol-% $[Rh(COD)_2]BF_4$. – [b] The yield was determined by GC using an internal standard (hexadecane).

$[Rh(COD_2)]BF_4$ was prepared according to literature procedures.[6] Spectra were recorded on: NMR: Bruker ARX 400; $CHCl_3/CDCl_3$ as internal reference; δ in ppm, *J* in Hz. – FT IR: Nicolet Magna 550. – MS: AMD 402. – M.p.: Büchi 535 apparatus; uncorrected values. – GC analysis: HP 6890 gas chromatograph using a HP-1 capillary column.

General Procedure for the Reaction of Amines with Aldehydes. — Catalytic Reaction without Oxidant (Method A): The Rh complex (0.055 mmol) and triphenylphosphane (0.11 mmol) were suspended in the corresponding solvent (5 mL). Amine and aldehyde were then added at room temperature as described in Table 1. The reaction mixture was heated in a pressure tube for 20 h at 100 °C in THF, or at 140 °C in toluene. The yield of products was determined by gas chromatography with hexadecane as the internal standard. The solvent was then removed in vacuo and the residue was dissolved in CH_2Cl_2 (20 mL) and extracted three times with HCl (5%). The amide was isolated from the oily residue of the organic phase by column chromatography (eluent: chloroform/methanol = 100:1).

In order to isolate the amine, the combined aqueous HCl phases were neutralized by the addition of NaOH (to pH = 9) and then extracted three times with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and the solvent was removed in vacuo. The amines were obtained after column chromatography (eluent: chloroform/methanol = 100:1).

Catalytic Reaction with Oxidant (Method B): The Rh complex (0.055 mmol), K_2CO_3 (0.22 mmol), and *N*-methylmorpholine *N*-oxide (2.20 mmol) were suspended in the corresponding solvent (5 mL). Amine and aldehyde were then added at room temperature as described in Table 2 and 3. The reaction mixture was heated in a pressure tube (8–20 h) at 100 °C (or 140 °C). Both the work up and purification were carried out according to method A.

***N*-Benzylmorpholine:**[7] Method A, colorless oil, yield (GC): 42%. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.44 (t, 4 H, NCH_2), 3.49 (s, 2 H, CH_2), 3.70 (t, 4 H, OCH_2), 7.31–7.34 (m, 5 H, Ph). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 53.5 (2 NCH_2), 63.4 (CH_2), 66.4 (2 OCH_2), 127.1, 128.2, 129.1 (CH, Ph), 137.7 (C, Ph). – MS (EI): *m/z* (%) = 177 (13) [M^+], 176 (100), 100 (25), 91 (23) [{$PhCH_2$}$^+$].

***N*-Benzoylmorpholine:**[8] Method B, colorless solid, m.p. 72 °C, yield (GC): 100%. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.22–3.96 (m, 8 H, CH_2), 7.4 (m, 5 H, Ph). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 42.5, 48.0 (NCH_2), 66.7 (2 OCH_2), 127.0, 128.4, 129.7 (CH, Ph), 135.2 (C, Ph), 170.3 (CO). – MS (EI): *m/z* (%) = 191 (21)

[M^+], 190 (39), 105 (100) [{PhCO}$^+$], 86 (12), 77 (53). − FT IR (KBr): $\tilde{\nu}$ = 1634 (C=O) cm^{-1}.

***N*-Benzylpiperidine:**[9] Method A, colorless oil, yield (GC): 34%. − ^1H NMR (400 MHz, $CDCl_3$): δ = 1.38−1.47 (m, 2 H, $NCH_2CH_2CH_2$), 1.57 (m, 4 H, NCH_2CH_2), 2.37 (m, 4 H, NCH_2), 3.47 (s, 2 H, NCH_2), 7.29−7.34 (m, 5 H, Ph). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.4 ($NCH_2CH_2CH_2$), 26.0 (NCH_2CH_2), 54.4 (NCH_2), 126.8, 128.0, 129.2 (CH, Ph), 138.6 (C, Ph). − MS (EI): *m/z* (%) = 175 (72) [M^+], 174 (70), 98 (58), 91 (100) [{$PhCH_2$}$^+$], 84 (53).

***N*-Benzoylpiperidine:**[10] Method B, colorless oil, yield (GC): 96%. − ^1H NMR (400 MHz, $CDCl_3$): δ = 1.50 (br m, 2 H, $NCH_2CH_2CH_2$), 1.66 (br m, 4 H, NCH_2CH_2), 3.32 (br m, 2 H, NCH_2), 3.69 (br m, 2 H, NCH_2), 7.37 (m, 5 H, Ph). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.5 ($NCH_2CH_2CH_2$), 25.6 and 26.5 (NCH_2CH_2), 43.0 and 48.7 (NCH_2), 126.7, 128.3, 129.3 (CH, Ph), 136.4 (C, Ph), 170.2 (CO). − MS (EI): *m/z* (%) = 189 (38) [M^+], 188 (100), 105 (78) [{PhCO}$^+$], 84 (6), 77 (43). − FT IR (neat): $\tilde{\nu}$ = 1632 (C=O) cm^{-1}.

***N*-Benzyl-*N*-butyl-*N*-methylamine:**[11] Method A, colorless oil, yield (GC): 23%. − ^1H NMR (400 MHz, $CDCl_3$): δ = 0.91 (t, 3 H, CH_3), 1.34 (m, 2 H, $NCH_2CH_2CH_2$), 1.51 (m, 2 H, NCH_2CH_2), 2.18 (s, 3 H, NCH_3), 2.37 (t, 2 H, NCH_2), 3.48 (s, 2 H, $PhCH_2$), 7.30−7.33 (m, 5 H, Ph). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0 (CH_3), 20.6 ($NCH_2CH_2CH_2$), 29.6 (NCH_2CH_2), 42.2 (NCH_3), 57.3 (NCH_2), 62.3 ($PhCH_2$), 126.8, 128.1, 129.0 (CH, Ph), 139.3 (C, Ph). − MS (CI, isobutane): *m/z* (%) = 177 (14) [M^+], 176 (100), 162 (7), 134 (15), 120 (28), 91(76) [{$PhCH_2$}$^+$].

***N*-Benzoyl-*N*-butyl-*N*-methylamine:**[12] Method B, colorless oil, yield (GC): 94%. − ^1H NMR (400 MHz, $CDCl_3$): δ = 0.74 and 0.93 (t, 3 H, CH_3), 1.10 and 1.36 (m, 2 H, $NCH_2CH_2CH_2$), 1.46 and 1.59 (m, 2 H, NCH_2CH_2), 2.87 and 3.01 (s, 3 H, NCH_3), 3.17 and 3.48 (t, 2 H, NCH_2), 7. 32 (m, 5 H, Ph). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.4 and 13.7 (CH_3), 19.4 and 19.9 ($NCH_2CH_2CH_2$), 28.9 and 30.1 (NCH_2CH_2), 32.5 and 37.2 (NCH_3), 47.0 and 50.8 (NCH_2), 126.4, 126.6, 128.1, 129.0 (CH, Ph), 136.6 (C, Ph), 171.0 and 171.7 (CO). − MS (EI): *m/z* (%) = 191 (10) [M^+], 105 (100) [{PhCO}$^+$], 77 (37). − FT IR (neat): $\tilde{\nu}$ = 1634 (C=O) cm^{-1}.

***N*-(4-Fluorobenzyl)morpholine:**[13] Method A, colorless oil, yield (GC): 6%. − ^1H NMR (400 MHz, $CDCl_3$): δ = 2.35 (t, ^3J = 4.6 Hz, 4 H, 2 NCH_2), 3.39 (s, 2 H, CH_2), 3.65 (t, 4 H, 2 OCH_2), 6.95, 7.20 (4 H, Ph). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 53.9 (2 NCH_2), 63.0 (CH_2), 67.4 (2 OCH_2), 115.4, 115.6, 131.0, 131.1 (CH, Ph), 133.9 (C, Ph), 163.7 (CF). − MS (CI, isobutane): *m/z* (%) = 196 (100) [$(MH)^+$], 164 (10), 109 (30).

***N*-(4-Fluorobenzoyl)morpholine:**[14] Method B, pale yellow oil, yield (GC): 94%. − ^1H NMR (400 MHz, $CDCl_3$): δ = 2.95 (m, br, 8 H, 4 CH_2), 7.0, 7.5 (4 H, Ph). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 67.3 (4 CH_2), 116.0, 116.2, 129.8, 129.9 (CH, Ph), 131.7 (C, Ph), 165.2 (CF), 169.9 (CO). − MS (CI, isobutane): *m/z* (%) = 210 (100) [$(MH)^+$], 123 (18). − FT IR (KBr): $\tilde{\nu}$ = 2962, 2923, 2855 (CH_2), 1636 (C=O), 1510, 1457, 1436 cm^{-1}.

4-Morpholinobenzaldehyde:[15] Method A (140 °C, toluene, aldehyde/amine = 2:1), pale yellow solid, m.p. 66 °C (EtOH), yield (GC): 30%. − ^1H NMR (400 MHz, $CDCl_3$): δ = 3.25 (t, ^3J = 4.4 Hz, 4 H, 2 × CH_2), 3.79 (t, ^3J = 4.4 Hz, 4 H, 2 × CH_2), 6.82, 7.69 (m, 4 H, Ph), 9.70 (CHO). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 47.7 (2 × NCH_2), 66.9 (2 × OCH_2), 113.9, 128.1, 132.2 (CH, Ph), 155.6 (C, Ph), 190.9 (CHO). − MS (CI, isobutane): *m/z* (%): 192 (100) [$(MH)^+$].

***N*-(4-Methoxybenzyl)morpholine:**[16] Method A, colorless oil, yield (GC): 38%. − ^1H NMR (400 MHz, $CDCl_3$): δ = 2.40 (t, ^3J = 4.4 Hz, 4 H, 2 × CH_2), 3.43 (s, 3 H, CH_3), 3.68 (t, ^3J = 4.4 Hz, 4 H, 2 × CH_2), 3.78 (s, 2 H, CH_2), 6.85, 7.23 (m, 4 H, Ph). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 54.0 (2 NCH_2), 55.7 (CH_3), 63.3 (CH_2), 67.5 (2 OCH_2), 114.0, 130.2 (CH, Ph), 130.8 (C, Ph), 159.2 ($COCH_3$). − MS (CI, isobutane): *m/z* (%) = 207 (44) [$(MH)^+$], 121 (100), 86 (18).

***N*-(4-Methoxybenzoyl)morpholine:**[3a] Method B, white solid, m.p. 42 °C, yield (GC): 84%. − ^1H NMR (400 MHz, $CDCl_3$): δ = 3.6 (br d, 8 H, 4 CH_2), 3.8 (s, 3 H, CH_3), 6.8, 7.3 (m, 4 H, Ph). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 54.4 (CH_3), 65.9 (4 CH_2), 112.8, 126.3, 128.2, (Ph), 159.9 ($COCH_3$) 169.4 (CO). −MS (CI, isobutane): *m/z* (%) = 222 (100) [$(MH)^+$], 135 (16). − FT IR (KBr): $\tilde{\nu}$ = 2963, 2921, 2854 (CH_2), 1635 (C=O), 1514, 1456, 1428 cm^{-1}.

***N*-(Cyclohexylmethyl)morpholine:**[17] Method A, colorless oil, yield (GC): 54%. − ^1H NMR (400 MHz, $CDCl_3$): δ = 0.80 (m, 2 H, H-4), 1.00−1.20 (m, 4 H, H-3), 1.40 (m, $^3J_{1,2}$ = 7.3 Hz, 1 H, H-1), 1.58−1.72 (m, 4 H, H-2), 2.04 (d, 2 H, CH_2), 2.30 (t, ^3J = 4.4 Hz, 4 H, 2 NCH_2), 3.60 (t, 4 H, 2 OCH_2). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.5 (C-3), 27.2 (C-4), 32.3 (C-2), 35.0 (C-1), 54.6 (2 NCH_2), 66.5 (CH_2), 67.4 (2 OCH_2). − MS (CI, isobutane): m/z (%) = 184 (100) [$(MH)^+$], 100 (92) [$M - C_6H_{11}^+$].

***N*-(Cyclohexylcarbonyl)morpholine:**[18] Method B, white solid, m.p. 86 °C (diethyl ether), yield (GC): 58%. − ^1H NMR (400 MHz, $CDCl_3$): δ = 1.15−1.26 (m, 4 H, H-3), 1.45 (m, 2 H, H-4), 1.60−1.76 (m, 4 H, H-2), 2.36 (m, 1 H, H-1), 3.40−3.60 (m, 8 H, 2 NCH_2, 2 OCH_2). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.2 (C-3, C-4), 29.7 (C-2), 40.7 (C-1), 42.3, 46.3 (2 NCH_2), 67.3, 67.5 (2 OCH_2), 175.1 (CO). − MS (CI, isobutane): *m/z* (%) = (198) (100) [$(MH)^+$]. − FT IR (KBr): $\tilde{\nu}$ = 1636 (C=O), 1444, 1360 cm^{-1}.

***N*-(2-Methylbenzyl)morpholine:**[16] Method A, colorless oil, yield (GC): 22%. − ^1H NMR (400 MHz, $CDCl_3$): δ = 2.30 (s, 3 H, CH_3), 2.38 (t, ^3J = 4.4 Hz, 4 H, 2 NCH_2), 3.39 (s, 2 H, CH_2), 3.62 (t, 4 H, 2 OCH_2), 7.05−7.15 (m, 4 H, Ph). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 53.9 (2 NCH_2), 63.0 (CH_2), 67.4 (2 OCH_2), 125.9, 127.6, 130.3, 130.7, 136.4 (CH, Ph), 138.0 (C, Ph). − MS (CI, isobutane): *m/z* (%) = 192 (100) [$(MH)^+$], 105 (14).

***N*-(2-Methylbenzoyl)morpholine:**[19] Method B, white solid, m.p. 43−44 °C, yield (GC): 100%. − ^1H NMR (400 MHz, $CDCl_3$): δ = 2.24 (s, 3 H, CH_3), 3.17 (m, 2 H, NCH_2), 3.51 (m, 2 H, NCH_2), 3.74 (m, ^3J = 4.8 Hz, 4 H, 2 OCH_2), 7.0−7.5 (m, 4 H, Ph). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.4 (CH_3), 42.3 (2 NCH_2), 47.7 (2 OCH_2), 126.2, 126.4, 129.5, 130.9, 134.6 (CH, Ph), 136.1 (C, Ph), 170.0 (CO). − MS (EI): *m/z* (%) = 205 (20) [M^+], 119 (100), 91 (46). − FT IR (KBr): $\tilde{\nu}$ = 2964, 2920, 2855 (CH_2), 1637 (C=O), 1490, 1430 cm^{-1}.

***N*-Octanoylmorpholine:**[20] Method B, colorless oil, yield (GC): 61%. − ^1H NMR (400 MHz, $CDCl_3$): δ = 0.86 (t, 3 H, CH_3), 1.29 (m, 8 H, 4 CH_2), 1.60 (m, ^3J = 7.6 Hz, 2 H, CH_2), 2.29 (t, 2 H, CH_2), 3.45 (t, 2 H, NCH_2), 3.57−3.67 (m, ^3J = 4.6 Hz, 6 H, NCH_2, 2 OCH_2). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.1 (CH_3), 21.6, 24.3, 28.1, 30.7, 32.1 (CH_2), 40.8, 45.0 (2 NCH_2), 65.7, 66.0 (2 OCH_2), 170.9 (CO). − MS (EI): *m/z* (%) = 213 (12) [M^+], 142 (28), 129 (100). − FT IR (KBr): $\tilde{\nu}$ = 2961, 2845 (CH_2), 1653 (C=O), 1430, 1116 cm^{-1}.

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