Tetrahedron 68 (2012) 2342–2348

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

One-pot stibine modified $Co_2(CO)_8$ catalyzed reductive N-alkylation of primary amides with carbonyl compounds

Laura Rubio-Pérez [a,*], Pankaj Sharma [a], F. Javier Pérez-Flores [a], Luis Velasco [a], J. Luis. Arias [b], Armando Cabrera [a]

[a] Instituto de Química, Universidad Nacional Autónoma de México, Ciudad Universitaria, Circuito Exterior, Coyoacán 04510, México D.F, Mexico
[b] Facultad de Estudios Superiores Cuautitlán, Departamento de Química, UNAM, Cuautitlán Izcalli, Estado de México 54700, Mexico

ARTICLE INFO

Article history:
Received 30 November 2011
Received in revised form 12 January 2012
Accepted 13 January 2012
Available online 21 January 2012

Keywords:
Secondary amides
Stibine ligands
Phosphine ligands
Cobalt catalysis
N-Alkylation

ABSTRACT

A one-pot stibine modified $Co_2(CO)_8$ homogeneous catalytic reductive N-alkylation of primary amides using aldehydes/ketones as alkylating agents, is reported. Good to excellent yields of a wide range of secondary amides are obtained (up to 97%) under relative mild conditions.

1. Introduction

Secondary amides are important intermediates for the production of bioactive compounds and play a crucial role in organic chemistry as versatile protecting groups for amines and carboxylic acids derivatives.[1–3] Up today, several methods with their merits and limitations are available for the synthesis of secondary amides, these include (a) coupling reaction of an acid chloride or a carboxylic acid with an amine,[4,5] (b) rearrangement of an oxime,[6] (c) transition metal catalyzed coupling of nitriles with an amine[7–9] or aryl halides with isocyanides,[10] (d) oxidative amination of aldehydes,[11] (e) direct amidation of alcohols and amines (known as dehydrogenative acylation),[12] and (f) coupling of terminal haloalkynes with amines.[13] In the last decades, the N-alkylation of primary amides with alcohols catalyzed by Lewis[14] or Bronsted acids[15] or by transition metals, such as Rh, Cu, Ru, and Ir, based on catalytic hydrogen-autotransfer (also called borrowing hydrogen) are also reported in the literature.[16,17] However, this reaction is limited to primary alcohols, which are activated in situ. Direct catalytic reductive N-alkylation of amides with carbonyl compounds represents an alternative for the preparation of secondary amides and opens the possibility to obtain prochiral compounds giving merit over the use of alcohols. Because of the low nucleophilicity of amides to react with carbonyl compounds, few satisfactory reports are currently available. Et_3SiH and trifluoroacetic acid have been used stoichiometrically to carry out this reaction.[18] To the best of our knowledge, the alkylation of amides using aldehydes and ketones as alkylating agents under homogeneous catalysis has not been explored, although two heterogeneous Pd/C catalyzed methods have been described.[19,20]

During the homogeneous hydroformylation and amidocarbonylation reactions of alkenes, a using triarylstibine-modified cobalt system, a competitive reduction process was also observed in our experiments.[21] In this paper, we report the first homogeneous triarylstibine-modified cobalt catalytic system for the one-pot syntheses of secondary amides by direct reductive N-alkylation of a variety of primary amides with aldehydes and ketones under hydrogen pressure.

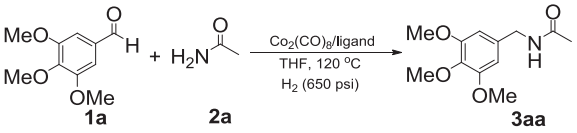
2. Results and discussion

In order to identify a suitable catalytic system, a series of mono stibines, mono- and bidentate phosphines ligands were evaluated in the reaction between 3,4,5-trimethoxybenzaldehyde (**1a**) and acetamide (**2a**) using $Co_2(CO)_8$ as catalyst under hydrogen pressure (Table 1). In the absence of catalyst, only 9% of the *N*-acyl imine was detected by GC–MS (entry 1). When the reaction was carried out in the presence of $Co_2(CO)_8$, the expected product **3aa** was isolated in

* Corresponding author. Tel.: +52 55 56224400/56224455; e-mail address: laurarpz@unam.mx (L. Rubio-Pérez).

0040-4020/$ – see front matter © 2012 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2012.01.038

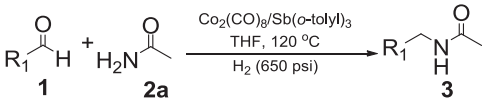
Table 1
Ligand screening for the reductive N-alkylation of acetamide[a] (**2a**)

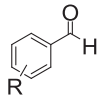
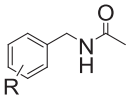
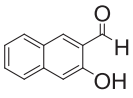
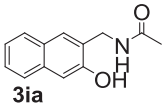
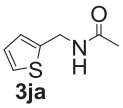
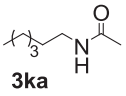


Entry	$Co_2(CO)_8$/Ligand	Time (h)	Yield[b] (%)
1	—	24	0[c]
2	$Co_2(CO)_8$	12	20
3	$Co_2(CO)_8$	20	45
4	$Co_2(CO)_8$	24	47
5	$Co_2(CO)_8/PBu_3$	24	23
6	$Co_2(CO)_8/PPh_3$	20	31
7	$Co_2(CO)_8/PPh_3$	24	35
8	$Co_2(CO)_8/P(o\text{-tolyl})_3$	12	22
9	$Co_2(CO)_8/P(o\text{-tolyl})_3$	20	52
10	$Co_2(CO)_8/P(o\text{-tolyl})_3$	24	54
11	$Co_2(CO)_8/P(p\text{-tolyl})_3$	24	46
12	$Co_2(CO)_8$/(*rac*)-BINAP	24	76
13	$Co_2(CO)_8$/(*rac*)-Tol-BINAP	24	73
14	$Co_2(CO)_8/SbPh_3$	24	46
15	$Co_2(CO)_8/Sb(o\text{-tolyl})_3$	24	0[d]
16	$Co_2(CO)_8/Sb(o\text{-tolyl})_3$	12	38
17	$Co_2(CO)_8/Sb(o\text{-tolyl})_3$	20	76
18	$Co_2(CO)_8/Sb(o\text{-tolyl})_3$	24	80
19	$Co_2(CO)_8/Sb(p\text{-tolyl})_3$	24	69

[a] Reaction conditions: **1a** (3.5 mmol), **2a** (3.5 mmol), $Co_2(CO)_8$ (0.12 mmol), ligand (0.12 mmol), 10 mL THF, H_2 (650 psi), 120 °C.
[b] Isolated yield.
[c] 9% of the corresponding *N*-acyl imine was detected by GC–MS.
[d] This reaction was carried out without hydrogen pressure, and 12% of *N*-acyl imine was detected by GC–MS.

Table 2
Reductive *N*-alkylation of acetamide (**2a**) with different aldehydes[a]



Entry	Aldehyde		Product	Yield[b] (%)
				
1	R=H	**1b**	**3ba**	82
2	R=4-Me	**1c**	**3ca**	81
3	R=4-OMe	**1d**	**3da**	82
4	R=4-*t*-Bu	**1e**	**3ea**	91
5	R=4-CN	**1f**	**3fa**	78
6	R=3,4-Me	**1g**	**3ga**	83
7	R=2,3,4-OMe	**1h**	**3ha**	79
8		**1i**	 **3ia**	71
9		**1j**	 **3ja**	80
10		**1k**	 **3ka**	61

[a] Reaction conditions: **1a** (3.5 mmol), **2a** (3.5 mmol), $Co_2(CO)_8$ (0.12 mmol), $Sb(o\text{-tolyl})_3$ (0.12 mmol), 10 mL THF, H_2 (650 psi), 120 °C, 24 h.
[b] Isolated yield.

a low yield after 12 h (entry 3). Increasing the reaction time up to 24 h, the yield was increased up to 47% (entries 3 and 4). Good yields were observed when triarylstibines were used as ligands in comparison to triarylphosphines (entries 14, 16–19 vs 5–11). A good π accepting character and trans effect of the antimony ligands may be responsible for the enhancement of exchange of ligands, giving the appropriate cobalt intermediates needed in the reductive N-alkylation process. In contrast, the substitution of monoxide ligands by monophosphines leads to a reaction rate decrease and promotes the generation of less active species. The reaction catalyzed by the alkylphosphine PBu_3 ligand was much less suitable than triarylphosphines, leading to the formation of **3aa** in 23% yield (entry 5); *rac*-BINAP and *rac*-tol-BINAP were effective in providing a good catalytic system (entries 12 and 13). Among the three monostibine ligands, $Sb(o\text{-tolyl})_3$ was the most effective to modify the cobalt catalytic system, affording the desired amide **3aa** in excellent yield after 24 h (80%, entry 18). For future experiments, this ligand was chosen to modify the cobalt catalyst.

Acetamide **2a** was reductively alkylated with different aldehydes in the presence of $Co_2(CO)_8$ and $Sb(o\text{-tolyl})_3$ under hydrogen pressure (Table 2). The reactions with mono-, di-, and trisubstituted benzaldehydes bearing either electron-donating (**1b**–**e** and **1g**–**h**) or electron-withdrawing (**1f**) substituents give **3ba**–**ha** in good to excellent yields (entries 1–7). Other aliphatic-, heteroaryl-, and aryl aldehydes could also be used as alkylating agents with good efficiency (entries 8–10). When the reaction was realized with **1i**, only **3ja** was isolated and any byproduct derived by the hydroxyl moiety cyclization with the amide group or the alkylation of the OH substituent with the amide was observed (entry 8).

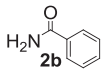
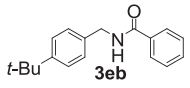
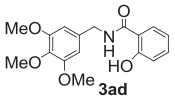
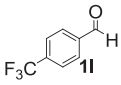
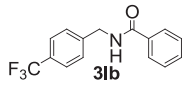
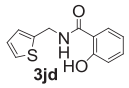
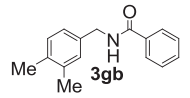
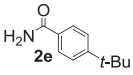
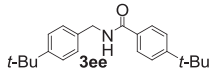
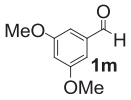
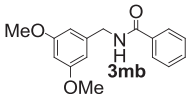
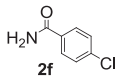
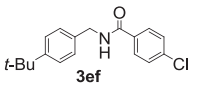
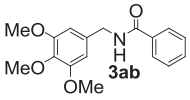
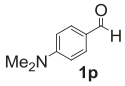
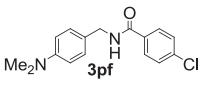
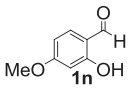
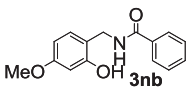
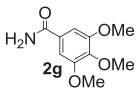
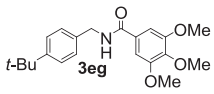
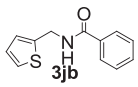
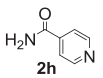
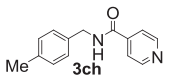
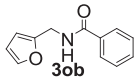
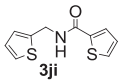
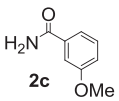
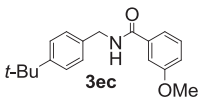
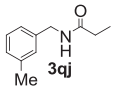
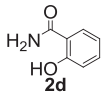
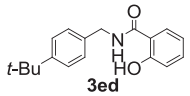
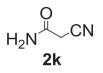
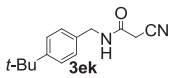
The direct reductive N-alkylation of a variety of aliphatic-, aryl-, and heteroaryl primary amides with substituted aryl aldehydes was also attempted (Table 3) and the desired products were isolated in good to excellent yields. Of all the aryl aldehydes used as alkylating agents, *p*-*tert*-butylbenzaldehyde (**1e**) was the most reactive providing secondary amides up to 97% yield (entries 1, 9, 13, 14, and 20). The reaction of **2b** proceeds well with a benzaldehyde substituted with two different electron-donating groups (OH and OMe) in an 86% yield (entry 6). *ortho*-, *meta*-, *para*-, and Trisubstituted benzamide derivatives could be successfully alkylated in satisfactory yields (entries 9–16), although a slightly lower yield was obtained when **2d** was used (entries 10–12). The steric effect of *ortho*-hydroxyl group on benzamide derivative may be responsible for this low yield. Combination of the primary heteroaryl amide **2j** with **1e** and **1j** gave the expected products **3ch** and **3ji** in 83% and 79% yield, respectively (entries 17 and 18). Under these conditions, aliphatic amides with or without the functional groups give excellent product yields (entries 19 and 20).[22]

The reaction of **2h** with two aliphatic aldehydes gave the corresponding secondary amides **3kh** and **3rh** in moderate yields (Scheme 1). The only byproducts isolated in significant amounts were *N*-acyl enamines of the corresponding products, providing evidence that these intermediates are relevant to form the secondary amide.

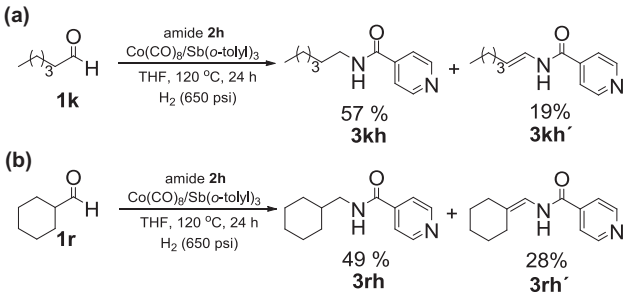
As revealed in Table 4, direct reductive alkylation of **2a** with some substituted acetophenone derivatives to synthesize prochiral secondary amides, moderate isolated yields were obtained. When the alkyl group of aryl ketone was changed from Me to Et, a slightly decrease in efficiency was observed (64 vs 56 yield).

Taking in consideration of isolation of enamides **3kh′** and **3rh′** (Scheme 1), a tentative catalytic cycle for N-alkylation of primary amides is proposed in Scheme 2, although kinetics experiments and details to confirm this reaction pathway are in process in our laboratory. The first step involves the formation of a cobalt hydride species **A** from $Co_2(CO)_8$, ligand and H_2. The condensation of carbonyl compound with primary amide affords an *N*-acyl enamine **B** (this intermediary is formed only when an aliphatic aldehyde

Table 3
Reductive N-alkylation of primary amides with aryl aldehydes[a]

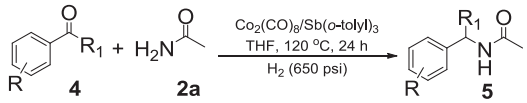
Entry	Substrates		Product	Yield (%)[b]	Entry	Substrates		Product	Yield (%)[b]
1	**1e**	 **2b**	 **3eb**	97	11	**1a**	**2d**	 **3ad**	69
2	 **1l**	**2b**	 **3lb**	79	12	**1j**	**2d**	 **3jd**	51
3	**1g**	**2b**	 **3gb**	81	13	**1e**	 **2e**	 **3ee**	92
4	 **1m**	**2b**	 **3mb**	85	14	**1e**	 **2f**	 **3ef**	94
5	**1a**	**2b**	 **3ab**	85	15	 **1p**	**2f**	 **3pf**	80
6	 **1n**	**2b**	 **3nb**	86	16	**1e**	 **2g**	 **3eg**	83
7	**1j**	**2b**	 **3jb**	81	17	**1c**	 **2h**	 **3ch**	83
8	 **1o**	**2b**	 **3ob**	79	18	**1j**	 **2i**	 **3ji**	79
9	**1e**	 **2c**	 **3ec**	93	19	 **1q**	 **2j**	 **3qj**	86
10	**1e**	 **2d**	 **3ed**	70	20	**1e**	 **2k**	 **3ek**	90

[a] Reaction conditions: **1a** (3.5 mmol), **2a** (3.5 mmol), $Co_2(CO)_8$ (0.12 mmol), Sb(*o*-tolyl)$_3$ (0.12 mmol), 10 mL THF, H_2 (650 psi), 120 °C, 24 h.
[b] Isolated yield.



Scheme 1. Reductive N-alkylation of **2h** with two aliphatic aldehydes.

Table 4
Reductive N-alkylation of **2a** with aryl ketones[a]

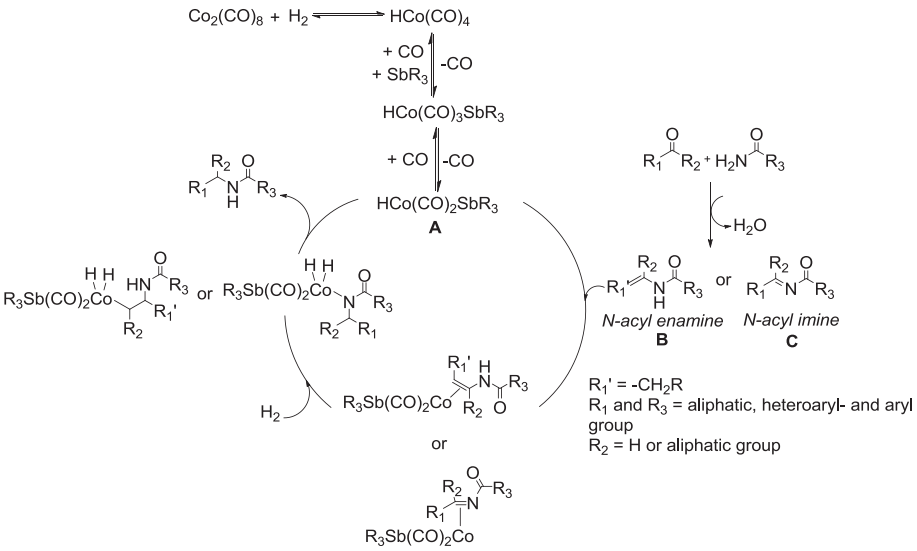


Entry	R	R_1		Product	Yield[b] (%)
1	H	Me	**4a**	**5aa**	64
2	4-Me	Me	**4b**	**5ba**	61
3	4-OMe	Me	**4c**	**5ca**	59
4	H	Et	**4d**	**5da**	56

[a] Reaction conditions: **4** (3.5 mmol), **2a** (3.5 mmol), $Co_2(CO)_8$ (0.12 mmol), Sb(*o*-tolyl)$_3$ (0.12 mmol), 10 mL THF, H_2 (650 psi), 120 °C.
[b] Isolated yield.

possesses an α hydrogen) or an *N*-acyl imine **C**. Species **B** or **C** coordinates to species **A** to give an amido cobalt species **D**. The oxidative addition of H_2 and later reductive elimination gives the secondary amide with the regeneration of the catalytic species **A**. It is important to note that under this reductive system, the mechanism proposed here is different than proposed when alcohols were used as alkylating agents.[25]

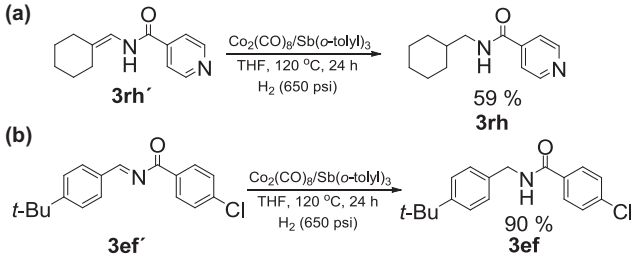
FT-IR spectra of the resultant solution of $Co_2(CO)_8/SbPPh_3$, $Co_2(CO)_8$/Sb(*o*-tolyl)$_3$ or $Co_2(CO)_8$/Sb(*p*-tolyl)$_3$ in THF under



Scheme 2. Tentative cycle catalytic for direct reductive N-alkylation.

hydrogen pressure at 120 °C for 10 h in the absence of substrate is in agreement with the existence of cobalt hydride specie of type $HCo(CO)_3SbR_3$ according to previous reports.[21b,23,24] When the resulting solution of $Co_2(CO)_8$/Sb(*o*-tolyl)$_3$ was concentrated under reduced pressure, an air sensitive black solid was isolated. This black solid was analyzed immediately by FAB-mass spectrometry giving two important fragments at *m*/*z* 537 and *m*/*z* 509 assigned to the species $HCo(CO)_3Sb$(*o*-tolyl)$_3$ and $HCo(CO)_2Sb$(*o*-tolyl)$_3$, respectively, these fragments were confirmed by HRMS (FAB) spectrometry. The IR spectra of this solid presented similar bands to that observed in solution. Solutions of $Co_2(CO)_8$/$SbPPh_3$ and $Co_2(CO)_8$/Sb(*o*-tolyl)$_3$ were successfully used in the model reaction of acetamide (**2a**) with 3,4,5-benzaldehyde (**1a**) obtaining similar yields as reported in Table 1.[26]

In addition, when *N*-acyl enamine **3rh′** (byproduct isolated) and *N*-acyl imine **3ef′** (synthesized and characterized) were subjected to the hydrogenation reactions under the same reaction conditions used for the reductive N-alkylation reaction, the secondary amides **3rh** and **3ef** were isolated in 59% and 90% yield, respectively (Scheme 3). These results indicate that formation of *N*-acyl enamine or *N*-acyl imine is the limiting step for direct reductive N-alkylation of primary amides.



Scheme 3. Hydrogenation of intermediates.

This stibine-modified cobalt catalyst tolerate the presence of sensitive functional groups, such as CF_3, Cl, NMe_2, and CN on either aldehyde or primary amide substrates without detectable reduction side products and in all tables, no reduction of carbonyl compound to alcohol was observed. Additionally, primary amides reacted faster with aryl aldehydes than aliphatic aldehydes and aryl ketones.

3. Conclusion

A new one-pot homogeneous catalytic reductive N-alkylation of a variety of primary amides using carbonyl compounds as alkylating agents is reported. This work offers some advantages: (a) relatively mild conditions, (b) carbonyl compounds are commercially available, and (c) good functional group tolerance. Expansion of this work related to the scope substrate, enantioselectivity and the confirmation of the mechanism proposed for this process are in progress.

4. Experimental section

4.1. General methods

All reactions were performed using standard Schlenk techniques. Catalytic reactions were performed on a 4712 Model Parr reactor. Flash column chromatographies were carried out on silica gel (70–230 mesh) from Merck. $Co_2(CO)_8$ was purchased from Stream Chemical Co. Unless otherwise noted, all reagents were obtained from commercial suppliers and used without further purification. THF was dried and deoxygenated prior to use by distillation under nitrogen over Na/benzophenone. Tri-*o*-tolylstibine, and tri-*p*-tolylstibine ligands were prepared according to the reported procedure.[27] Required starting primary amides: 2-thiophenecarboxamide, 3-methoxybenzamide, and *p*-*tert*-butylbenzamide were synthesized from the parent aldehyde and hydroxylamine hydrochloride using the protocol described by Gowda and Chakraborty.[28] Melting points were determined using a Mel-Temp II apparatus in open capillaries and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a JEOL GX-300 or Bruker-Avance 300 (300 MHz for ^{1}H and 75 MHz for ^{13}C, respectively), Bruker-Avance 400 (400 for ^{1}H and 100 MHz for ^{13}C, respectively) and Varian-Inova 500 (500 for ^{1}H and 125 MHz for ^{13}C, respectively) instruments in $CDCl_3$ or acetone-d_6 solvents using Me_4Si (δ=0 ppm) as an internal reference. All chemical shifts are reported in parts per million (δ) and coupling constants (J) are reported in hertz (Hz) to apparent peak multiplications. IR spectra were measured in $CHCl_3$ solutions or in KBr pellets on a Nicolet FTIR Magna 750 spectrophotometer and the absorption frequencies are given in cm^{-1}. HRMS was obtained with a JEOL JMS-AX505-A (EI mode at 70 eV) and JEOL JMS-SX 102 A (FAB mode)

mass spectrometers and the elemental compositions were calculated within an uncertainty of 5 ppm by using the program installed in the computer system.

4.2. General procedure for N-alkylation of primary amides with aldehydes (Tables 2 and 3)

Corresponding aldehyde (3.5 mmol) and 3.5 mmol of primary amide derivative were added to a solution of 0.12 mmol of $Co_2(CO)_8$ and 0.12 mmol of ligand (R_3Sb or R_3P) in 10 mL of dry THF and was stirred under nitrogen for 5 min in a Schlenk tube. The solution was transferred to a 45 mL stainless steel reactor (PARR) previously purged with vacuum-nitrogen. The reaction vessel was pressurized with H_2 at 650 psi (45 bar), subsequently it was immersed in an oil bath with stir and warmed at 120 °C during 24 h. At the end of this time, the reactor was cooled and the gas was liberated. The solution was concentrated under reduced pressure and the resulting residue was purified by column chromatography on silica gel (70–230 mesh) with an appropriate mixture of hexane/ethyl acetate as eluent to afford the corresponding secondary amide. The products **3ba**,[3] **3ca**,[4] **3da**,[4] **3ga**,[6f] **3ja**,[29] **3ka**,[30] **3jb**,[31] **3ob**,[32] and **3ed**[33] are known and were identified by NMR spectra. Characterizations of the rest of the products are as follows.

*4.2.1. N-(3,4,5-Trimethoxylbenzyl)acetamide (**3aa**).* White solid, yield: 80%; mp 81–84 °C. IR (sol $CHCl_3$) 3448, 1669, 1506. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.43 (s, 2H, ArH), 6.16 (br, 1H, NH), 4.29 (d, J=5.5 Hz, 2H, CH_2), 3.79 (s, 6H), 3.77 (s, 3H, OMe), 1.99 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0 (CO), 153.3, 137.1, 134.1, 104.9, 60.8 (OMe), 56.1 (OMe), 44.0 (CH_2), 23.2 (CH_3). HRMS (EI): m/z $[M]^+$ calcd for $C_{12}H_{17}NO_4$, 239.1158; found, 239.1153.

*4.2.2. N-(4-tert-Butylbenzyl)acetamide (**3ea**).* Colorless crystals yield: 91%; mp 75–78 °C. IR (sol $CHCl_3$) 3444, 1647, 1513. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (d, J=8.5 Hz, 2H, ArH), 7.20 (d, J=8.5 Hz, 2H, ArH), 6.29 (br, 1H, NH), 4.36 (d, J=5.2 Hz, 2H, CH_2), 1.99 (s, 3H, CH_3), 1.29 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4 (CO), 150.6, 135.0, 127.7, 125.6, 43.6 (CH_2), 34.5 [**C**$(CH_3)_3$], 31.3 [C(**C**$H_3)_3$], 23.0 (CH_3). HRMS (EI): m/z $[M]^+$ calcd for $C_{13}H_{19}NO$, 205.1467; found, 205.1467.

*4.2.3. N-(2,3,4-Trimethoxylbenzyl)acetamide (**3ha**).* Light yellow solid, yield: 79%; mp 79–82 °C. IR (sol $CHCl_3$) 3448, 1664, 1517. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.95 (d, J=8.2 Hz, 1H, ArH), 6.60 (d, J=8.2 Hz, 1H, ArH), 6.02 (br, 1H, NH), 4.33 (d, J=5.7 Hz, 2H, CH_2), 3.90 (s, 3H, OMe), 3.85 (s, 3H, OMe), 3.82 (s, 3H, OMe), 1.95 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.8 (CO), 153.5, 151.9, 142.1, 124.1, 124.0, 107.2, 61.0 (OMe), 60.8 (OMe), 56.0 (OMe), 39.1 (CH_2), 23.3 (CH_3). HRMS (EI): m/z $[M]^+$ calcd for $C_{12}H_{17}NO_4$, 239.1158; found, 239.1153.

*4.2.4. N-[(3-Hydroxynaphthalen-2-yl)methyl]acetamide (**3ia**).* Light yellow solid, yield: 71%; mp 164–167 °C. IR (KBr) 3296, 1650, 1571. ^{1}H NMR (300 MHz, acetone-d_6) δ 10.44 (s, 1H, OH), 8.52 (br, 1H, NH), 8.01 (d, J=8.5 Hz, 1H, ArH), 7.80–7.73 (m, 2H, ArH), 7.48–7.43 (m, 1H, ArH), 7.32–7.27 (m,1H, ArH), 7.13 (d, J=8.8 Hz, 1H, ArH), 4.72 (d, J=5.7 Hz, 2H, CH_2), 1.95 (s, 3H, CH_3). ^{13}C NMR (75 MHz, acetone-d_6) δ 172.7 (CO), 154.6, 133.5, 129.7, 129.0, 128.5, 126.5, 122.8, 122.2, 120.1, 118.9, 34.7 (CH_2), 21.4 (CH_3). HRMS (EI): m/z $[M]^+$ calcd for $C_{13}H_{13}NO_2$, 215.0946; found, 215.0950.

*4.2.5. N-(4-tert-Butylbenzyl)benzamide (**3eb**).* White solid, yield: 97%, mp 115–116 °C. IR (sol $CHCl_3$) 3451, 1658, 1516. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, J=8.4 Hz, 2H, ArH), 7.41–7.20 (m, 6H, ArH), 7.23–7.17 (m, 1H, ArH), 6.39 (br, 1H, NH), 4.53 (d, J=5.7 Hz, 2H, CH_2), 1.23 [s, 9H, $C(CH_3)_3$]. ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.3 (CO), 150.7, 135.1, 134.4, 131.5, 128.6, 127.8, 127.0, 125.7, 43.8 (CH_2), 34.5 [**C**$(CH_3)_3$], 31.3 [C(**C**$H_3)_3$]. HRMS (FAB$^+$): m/z $[M+H]^+$ calcd for $C_{18}H_{22}NO$, 268.1701; found, 268.1700.

*4.2.6. N-(4-Trifluoromethylbenzyl)benzamide (**3lb**).* White solid, yield: 79%, mp 131–134 °C. IR (sol $CHCl_3$) 3454, 1663, 1518. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, J=7.5 Hz, 2H, ArH), 7.59 (d, J=7.8 Hz, 2H, ArH), 7.53 (d, J=7.2 Hz, 1H, ArH), 7.46–7.41 (m, 4H, ArH), 6.90 (br, 1H, NH), 4.68 (d, J=5.7 Hz, 2H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.6 (CO), 142.4, 133.9, 131.8, 129.9, 128.6, 127.9, 125.6 (q, J=271 Hz), 122.3, 43.4 (CH_2). HRMS (EI): m/z $[M]^+$ calcd for $C_{15}H_{12}NOF_3$, 279.0871; found, 279.0869.

*4.2.7. N-(3,4-Dimethylbenzyl)benzamide (**3gb**).* Colorless crystals, yield: 81%; mp 118–121 °C. IR (sol $CHCl_3$) 3451, 1657, 1518. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (d, J=7.8 Hz, 2H, ArH), 7.54–7.49 (m, 1H, ArH), 7.45–7.43 (m, 2H, ArH), 7.15–7.09 (m, 3H, ArH), 6.75 (br, 1H, NH), 4.58 (d, J=5.1 Hz, 2H, CH_2), 2.28 (s, 3H, Me), 2.28 (s, 3H, Me). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.3 (CO), 137.0, 135.9, 135.6, 134.4, 131.4, 129.9, 129.3, 128.5, 127.0, 125.4, 43.9 (CH_2), 19.8 (Me), 19.4 (Me). HRMS (EI): m/z $[M]^+$ calcd for $C_{16}H_{17}NO$, 239.1310; found, 239.1312.

*4.2.8. N-(3,5-Dimethoxybenzyl)benzamide (**3mb**).* White solid, yield: 85%; mp 104–106 °C. IR (sol $CHCl_3$) 3451, 1660, 1518. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, J=7.8 Hz, 2H, ArH), 7.54–7.49 (m, 1H, ArH), 7.46–7.41 (m, 2H, ArH), 6.64 (br, 1H, NH), 6.51 (s, 2H, ArH), 6.4 (s, 1H, ArH), 4.58 (d, J=5.7 Hz, 2H, CH_2), 3.79 (s, 6H, OMe). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.4 (CO), 161.1, 140.6, 134.3, 131.5, 128.6, 127.0, 105.8, 99.4, 55.3 (OMe), 44.2 (CH_2). HRMS (EI): m/z $[M]^+$ calcd for $C_{16}H_{17}NO_3$, 271.1208; found, 271.1212.

*4.2.9. N-(3,4,5-Trimethoxybenzyl)benzamide (**3ab**).* White solid, yield: 85%; mp 92–95 °C. IR (sol $CHCl_3$) 3451, 1658, 1508. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (d, J=7.8 Hz, 2H, ArH), 7.49–7.45 (m, 1H, ArH), 7.40–7.35 (m, 2H, ArH), 7.21 (br, 1H, NH), 6.51 (s, 2H, ArH), 4.50 (d, J=5.7 Hz, 2H, CH_2), 3.77 (s, 3H, OMe), 3.75 (s, 6H, OMe). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.5 (CO), 153.2, 136.9, 134.3, 134.2, 131.5, 128.5, 127.1, 104.7, 60.8 (OMe), 55.9 (OMe), 44.3 (CH_2). HRMS (EI): m/z $[M]^+$ calcd for $C_{17}H_{19}NO_4$, 301.1314; found, 301.1314.

*4.2.10. N-[(2-Hydroxy-4-methoxy)benzyl]benzamide (**3nb**).* Yellow solid, yield: 86%, mp 100–103 °C. IR (sol $CHCl_3$) 3452, 3149, 1630, 1528. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.83 (br, 1H, –OH), 7.78–7.76 (m, 2H, ArH), 7.54–7.48 (m, 1H, ArH), 7.42–7.40 (m, 2H, ArH), 7.37 (br, 1H, NH), 7.06 (d, J=8.4 Hz, 1H, ArH), 6.54 (d, J=2.7 Hz, 1H, ArH), 6.41 (dd, J=8.4, 2.7 Hz, 1H, ArH), 4.51 (d, J=6.3 Hz, 2H, CH_2), 3.76 (s, 3H, OMe). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.8 (CO), 161.2, 157.1, 132.7, 132.2, 131.6, 128.7, 127.2, 116.7, 106.3, 102.8, 55.3 (OMe), 40.5 (CH_2). HRMS (EI): m/z $[M]^+$ calcd for $C_{15}H_{15}NO_3$, 257.1052; found, 257.1049.

*4.2.11. N-(4-tert-Butylbenzyl)-3-methoxybenzamide (**3ec**).* White solid, yield: 93%, mp 130–133 °C. IR (sol $CHCl_3$) 3449, 1658, 1516. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43–7.39 (m, 3H, ArH), 7.32–7.28 (m, 4H, ArH), 7.08–7.03 (m, 1H, ArH), 6.60 (br, 1H, NH), 4.63 (d, J=5.7 Hz, 2H, CH_2), 3.85 (s, 3H, OMe), 1.35 [s, 9H, $C(CH_3)_3$]. ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.2 (CO), 159.8, 150.6, 135.9, 135.1, 129.5, 127.7, 125.7, 118.7, 117.8, 112.3, 55.4 (OMe), 43.9 (CH_2), 34.5 [**C**$(CH_3)_3$], 31.3 [C(**C**$H_3)_3$]. HRMS (EI): m/z $[M]^+$ calcd for $C_{19}H_{23}NO_2$, 297.1729; found, 297.1733.

*4.2.12. 2-Hydroxy-N-(3,4,5-trimethoxybenzyl)benzamide (**3ad**).* White solid, yield: 69%, mp 110–113 °C. IR (KBr) 3358, 1640, 1528. ^{1}H NMR (300 MHz, acetone-d_6) δ 12.76 (br, 1H, OH), 8.59 (br, 1H, NH), 7.87–7.83 (m, 1H, ArH), 7.47–7.41 (m, 1H, ArH), 6.95–6.85 (m, 2H

ArH), 6.74 (s, 2H, ArH), 4.58 (d, J=6.0 Hz, 2H, CH_2), 3.82 (s, 6H, OMe), 3.72 (s, 3H, OMe). ^{13}C NMR (75 MHz, acetone-d_6) δ 171.0 (CO), 163.2, 154.4, 138.4, 134.8, 128.3, 127.5, 119.3, 118.7, 115.4, 106.1, 60.5 (OMe), 56.4 (OMe), 43.9 (CH_2). HRMS (EI): m/z [M]$^+$ calcd for $C_{17}H_{19}NO_5$, 317.1263; found, 317.1262.

*4.2.13. 2-Hydroxy-N-(thiophen-2-ylmethyl)benzamide (**3jd**).* Colorless crystals, yield: 51%, mp 151–154 °C. IR (KBr) 3358, 1640, 1543. ^{1}H NMR (300 MHz, acetone-d_6) δ 12.68 (br, 1H, OH), 8.76 (br, 1H, NH), 7.82 (dd, J=8.1, 1.5 Hz, 1H ArH), 7.44 (td, J=8.1, 1.5 Hz, 1H ArH), 7.36 (dd, J=8.1, 1.2 Hz, 1H ArH), 7.10–7.09 (m, 1H, ArH), 6.99–6.85 (m, 3H, ArH), 4.81 (d, J=5.7 Hz, 2H, CH_2). ^{13}C NMR (75 MHz, acetone-d_6) δ 170.9 (CO), 162.7, 142.4, 134.9, 127.5, 126.9, 126.0, 119.4, 119.3, 118.7, 115.2, 38.2 (CH_2). HRMS (EI): m/z [M]$^+$ calcd for $C_{12}H_{11}NO_2S$, 233.0511; found, 233.0509.

*4.2.14. 4-tert-Butyl-N-(4-tert-butylbenzyl)benzamide (**3ee**).* White solid, yield: 92%, mp 108–111 °C. IR (sol $CHCl_3$) 3451, 1655, 1525. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (d, J=8.4 Hz, 2H, ArH), 7.45 (d, J=8.4 Hz, 2H, ArH), 7.40 (d, J=8.4 Hz, 2H, ArH), 7.35 (d, J=8.2 Hz, 2H, ArH), 7.05 (br, 1H, NH), 4.62 (d, J=5.4 Hz, 2H, CH_2), 1.38 [s, 9H, $C(CH_3)_3$], 1.37 [s, 9H, $C(CH_3)_3$]. ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.3 (CO), 155.0, 150.5, 135.3, 131.5, 127.7, 126.9, 125.6, 125.5, 43.7 (CH_2), 34.9 [**C**$(CH_3)_3$], 34.5 [**C**$(CH_3)_3$], 31.3 [C(**C**$H_3)_3$], 31.2 [C(**C**$H_3)_3$]. HRMS (EI): m/z [M]$^+$ calcd for $C_{22}H_{29}NO$, 323.2249; found, 323.2255.

*4.2.15. N-(4-tert-Butylbenzyl)-4-chlorobenzamide (**3ef**).* White solid, yield: 94%, mp 138–141 °C. IR (sol $CHCl_3$) 3450, 1660, 1596, 1516. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, J=8.7 Hz, 2H, ArH), 7.40 (d, J=8.4 Hz, 2H, ArH), 7.38 (d, J=8.7 Hz, 2H, ArH), 7.30 (d, J=8.4 Hz, 2H, ArH), 6.68 (br, 1H, NH), 4.60 (d, J=5.4 Hz, 2H, CH_2), 1.35 [s, 9H, $C(CH_3)_3$]. ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.3 (CO), 150.7, 137.7, 134.9, 132.8, 128.8, 128.4, 127.7, 125.7, 43.9 (CH_2), 34.5 [**C**$(CH_3)_3$], 31.3 [C(**C**$H_3)_3$]. HRMS (EI): m/z [M]$^+$ calcd for $C_{18}H_{20}ClNO$, 301.1233; found, 301.1228.

*4.2.16. 4-Chloro-N-[(4-dimethylamino)benzyl]benzamide (**3pf**).* Colorless crystals, yield: 80%, mp 148–151 °C. IR (sol $CHCl_3$) 3450, 1659, 1596, 1521. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (d, J=8.7 Hz, 2H, ArH), 7.38 (d, J=8.7 Hz, 2H, ArH), 7.24 (d, J=8.7 Hz, 2H, ArH), 6.74 (d, J=8.4 Hz, 2H, ArH), 6.53 (br, 1H, NH), 4.52 (d, J=5.4 Hz, 2H, CH_2), 2.91 [s, 6H, NMe_2]. ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.1 (CO), 150.1, 137.5, 132.9, 129.2, 128.7, 128.4, 125.7, 112.8, 43.9 (CH_2), 40.7 (NMe_2). HRMS (EI): m/z [M]$^+$ calcd for $C_{16}H_{17}ClN_2O$, 288.1029; found, 288.1034.

*4.2.17. N-(4-tert-Butylbenzyl)-3,4,5-trimethoxybenzamide (**3eg**).* Colorless oil, yield: 83%. IR (sol $CHCl_3$) 3449, 1656, 1586, 1522. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (d, J=8.4 Hz, 2H, ArH), 7.30 (d, J=8.4 Hz, 2H, ArH), 7.06 (s, 2H, ArH), 6.72 (br, 1H, NH), 4.60 (d, J=5.4 Hz, 2H, CH_2), 3.88 (s, 3H, OMe), 3.87 (s, 6H, OMe), 1.33 [s, 9H, $C(CH_3)_3$]. ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1 (CO), 153.1, 150.6, 140.8, 135.2, 129.8, 127.7, 125.6, 104.4, 60.9 (OMe), 56.2 (OMe), 43.9 (CH_2), 34.5 [**C**$(CH_3)_3$], 31.3 [C(**C**$H_3)_3$]. HRMS (EI): m/z [M]$^+$ calcd for $C_{21}H_{27}NO_4$, 357.1940; found, 357.1939.

*4.2.18. N-(4-Methylbenzyl)-4-pyridinecarboxamide (**3ch**).* White solid, yield: 83%, mp 128–130 °C. IR (sol $CHCl_3$) 3447, 1669, 1518. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (d, J=5.6 Hz, 2H, ArH), 7.60 (d, J=5.6 Hz, 2H, ArH), 7.22 (d, J=8.0 Hz, 2H, ArH), 7.15 (d, J=8.0 Hz, 2H, ArH), 6.77 (br, 1H, NH), 4.57 (d, J=5.6 Hz, 2H, CH_2), 2.34 (s, 3H, Me). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2 (CO), 150.3, 141.5, 137.6, 134.4, 129.5, 127.9, 120.9, 44.0 (CH_2), 21.0 (Me). HRMS (FAB$^+$): m/z [M+H]$^+$ calcd for $C_{14}H_{15}N_2O$, 227.1184; found, 227.1188.

*4.2.19. N-(Thiophen-2-ylmethyl)-2-thiophenecarboxamide (**3ji**).* Colorless needles, yield: 79%; mp 111–114 °C. IR (sol $CHCl_3$) 3447, 1650, 1532, 1501. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55–7.50 (m, 2H, ArH), 7.29–7.26 (m, 1H, ArH), 7.11–7.06 (m, 2H, ArH), 7.01–6.98 (m, 1H, ArH), 6.44 (br, 1H, NH), 4.81 (d, J=5.4 Hz, 2H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.5 (CO), 140.5, 138.4, 130.2, 128.3, 127.6, 127.0, 126.4, 125.4, 38.7 (CH_2). HRMS (EI): m/z [M]$^+$ calcd for $C_{10}H_9NOS_2$, 223.0126; found, 223.0131.

*4.2.20. N-(3-Methylbenzyl)propionamide (**3qj**).* Light yellow oil, yield: 86%. IR (sol $CHCl_3$) 3447, 1666, 1514. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29–7.18 (m, 1H, ArH), 7.08–7.04 (m, 3H, ArH), 6.50 (br, 1H, NH), 4.34 (d, J=5.7 Hz, 2H, CH_2), 2.33 (s, 3H, Me), 2.23 (q, 2H, J=7.5 Hz, CH_2), 1.15 (t, 3H, J=7.5 Hz, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.0 (CO), 138.4, 138.2, 128.52, 128.50, 128.0, 124.7, 43.4 (CH_2), 29.5 (CH_2), 21.3 (Me), 9.9 (CH_3). HRMS (EI): m/z [M]$^+$ calcd for $C_{11}H_{15}NO$, 177.1154; found, 177.1155.

*4.2.21. N-(4-tert-Butylbenzyl)-2-cyanoacetamide (**3ek**).* White solid, yield: 90%; mp 128–131 °C. IR (sol $CHCl_3$) 3515, 2245 (CN), 1705, 1593, 1515. ^{1}H NMR (300 MHz, $CDCl_3$) 7.39 (d, J=8.4 Hz, 2H, ArH), 7.25 (d, J=8.4 Hz, 2H, ArH), 6.17 (br, 1H, NH), 3.66 (d, J=5.7 Hz, 2H, CH_2), 3.28 (d, J=5.1 Hz, 1H, CH_2), 3.21 (d, J=5.1 Hz, 1H, CH_2), 1.34 [s, 9H, $C(CH_3)_3$]. ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4 (CO), 150.7, 132.4, 128.8, 125.8, 117.9 (–CN), 40.4 (CH_2), 35.2 (CH_2), 34.5 [**C**$(CH_3)_3$], 31.3 [C(**C**$H_3)_3$]. HRMS (EI): m/z [M]$^+$ calcd for $C_{14}H_{18}N_2O$, 230.1419; found, 230.1425.

*4.2.22. N-Hexyl-4-pyridinecarboxamide (**3kh**).* Colorless needles, yield: 57%, mp 58–61 °C IR (sol $CHCl_3$) 3448, 1670, 1523. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (d, J=5.2 Hz, 2H, ArH), 7.81 (d, J=5.2 Hz, 2H, ArH), 6.69 (br, 1H, NH), 3.50–3.45 (m, 2H, CH_2), 1.68–1.60 (m, 2H, CH_2), 1.40–1.25 (m, 6H, CH_2), 0.89 (t, J=6.8 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6 (CO), 148.4, 144.0, 121.9, 40.4 (CH_2NH), 31.4, 29.4, 26.6, 22.5 (CH_2), 13.9 (Me). HRMS (EI): m/z [M]$^+$ calcd for $C_{12}H_{18}N_2O$, 206.1419; found, 206.1420.

*4.2.23. N-(Hexen-1-yl)-4-pyridinecarboxamide (**3kh′**).* White solid, yield: 19%, mp 56–59 °C. IR (sol $CHCl_3$) 3452, 2933, 2855, 1665, 1505, 1483. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.76 (d, J=5.5 Hz, 2H, ArH), 8.15 (d, J=10.0 Hz, 1H, NH), 7.56 (d, J=5.5 Hz, 2H, ArH), 6.95–6.89 (m, 1H, CH=C**H**NH), 5.48–5.43 (m, 1H, C**H**=CHNH), 2.12–2.07 (m, 2H, CH_2), 1.41–1.30 (m, 4H, CH_2), 0.91 (t, J=7.2 Hz, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.8 (CO), 149.6, 140.8, 122.2 (CH=**C**HNH), 121.4, 116.4 (**C**H=CHNH), 31.8, 29.4, 22.0 (CH_2), 13.8 (CH_3). HRMS (EI): m/z [M]$^+$ calcd for $C_{12}H_{16}N_2O$, 204.1263; found, 204.1459.

*4.2.24. N-Cyclohexylmethyl-4-pyridinecarboxamide (**3rh**).* White solid, yield: 49%, mp 106–108 °C. IR (sol $CHCl_3$) 3453, 1667, 1522. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (d, J=5.0 Hz, 2H, ArH), 7.59 (dd, J=5.0, 1.6 Hz, 2H, ArH), 6.54 (br, 1H, NH), 3.28 (t, J=6.2 Hz, 2H, CH_2), 2.07–1.80 (m, 1H, C**H**CH_2), 1.79–1.52 (m, 7H, CH_2), 1.28–1.12 (m, 3H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6 (CO), 150.3, 141.9, 120.9, 46.3 (**C**HCH_2), 37.8, 30.8, 26.2, 25.7 (CH_2). HRMS (EI): m/z [M]$^+$ calcd for $C_{13}H_{18}N_2O$, 218.1419; found, 218.1423.

*4.2.25. N-(Cyclohexylidenemethyl)-4-pyridinecarboxamide (**3kh′**).* White solid, yield: 28%. IR (sol $CHCl_3$) 3453, 2934, 2857, 1667, 1506, 1483. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (d, J=5.6 Hz, 2H, ArH), 7.63–7.61 (m, 3H, NH+ArH), 6.69 (d, J=10.1 Hz, 1H, CH=C**H**NH), 2.17–2.14 (m, 4H, CH_2), 1.59–1.57 (m, 6H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.3 (CO), 150.6, 141.3, 126.2 (CH=**C**HNH), 120.7, 113.7 (**C**H=CHNH), 27.9, 27.7, 26.9, 26.4 (CH_2). HRMS (EI): m/z [M]$^+$ calcd for $C_{13}H_{16}N_2O$, 216.1263; found, 216.1266.

4.3. General procedure for N-alkylation of acetamide with ketones (Table 4)

The procedure was the same for N-alkylation of primary amides with aldehydes. The crude product was purified by column

chromatography on silica gel (70–230 mesh) with a mixture of hexane/ethyl acetate (6/4) as eluent to afford the corresponding secondary amide. The products **5aa**,[6f] **5ba**,[6f] **5ca**,[6f] are known and were identified by NMR spectra. Characterization of **5da** is as follows.

*4.3.1. N-(1-Phenylpropyl)acetamide (**5da**).* Colorless oil, yield: 56%. IR (sol $CHCl_3$) 3441, 1663, 1512. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34–7.22 (m, 5H, ArH), 5.76 (br, 1H, NH), 4.91–4.84 (m, 1H, $CHCH_3$), 1.91 (s, 3H, CH_3CO), 1.87–1.75 (m, CH_3CH_2), 0.87 (t, J=7.1 Hz, 3H, CH_3CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.3 (CO), 158.9, 141.5, 135.3, 127.5, 114.0, 55.3 (OMe), 48.2 ($CHCH_3$), 23.5 (CH_3CO), 21.6 (CH_3CH). HRMS (EI): m/z $[M]^+$ calcd for $C_{11}H_{15}NO$, 177.1154; found, 177.1151.

4.4. Preparation of *N*-acyl imine 3ef′

This compound was prepared utilizing a modified procedure to that of Yamaguchi.[17c] In a flask equipped with a magnetic stir bar were added 25 mmol of *p*-chlorobenzamide, 25 mmol of *p*-toluene sulfinic acid sodium salt monohydrate, 40 mL of methanol, 80 mL of water, and 17 mmol of *p*-*tert*-butylbenzaldehyde sequentially. The mixture was stirred at 50 °C for 120 h. The resulting precipitated was isolated by Büchner funnel filtration and then was washing with diethyl ether (2×100 mL). The white crude solid (α-amido sulfone) was dried in vacuo and used without further purification. To a round flask were added 10 mmol of Cs_2CO_3 and 10 mmol of Na_2SO_4. These solids were flame-dried under high vacuum and allowed to cool. Then, were added 40 mL of CH_2Cl_2 and 2 mmol of the α-amido sulfone. After stirring at 23 °C for 8 h, 40 mL of hexanes was added and the mixture was filtered through a pad of Celite. The Celite was rinsed with CH_2Cl_2 (2×60 mL). Removal of solvent in vacuo provided pure *N*-acyl enamine **3ef′**.

*4.4.1. N-(4-tert-Butylbenzylidene)-4-chlorobenzamide (**3ef′**).* White solid, yield: 47%. IR (film) 2966, 2867, 1649, 1595, 1523, 1481. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.88 (s, 1H, iminic CH), 7.73 (d, J=8.1 Hz, 2H, ArH), 7.66 (d, J=8.1 Hz, 2H, ArH), 7.46 (d, J=8.1 Hz, 2H, ArH), 7.31 (d, J=8.1 Hz, 2H, ArH), 1.27 [s, 9H, $C(CH_3)_3$]. ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.1 (CO), 166.3 (CH=N), 151.7, 138.2, 136.1, 129.7, 128.9, 128.6, 125.6, 34.6 [**C**$(CH_3)_3$], 31.3 [C(**C**$H_3)_3$]. HRMS (FAB): m/z $[M]^+$ calcd for $C_{18}H_{19}ClNO$, 300.1155; found, 300.1151.

4.5. Hydrogenation of *N*-acyl enamine 3rh′ and *N*-acyl imine 3ef′ by $Co_2(CO)_8$/Sb(*o*-tolyl)$_3$ system (Scheme 3)

N-acyl enamine (**3rh′**) or *N*-acyl imine (**3ef′**) (1.75 mmol) was added to a solution of 0.12 mmol of $Co_2(CO)_8$ and 0.12 mmol of Sb(*o*-tolyl)$_3$ in 10 mL of dry THF and was stirred under nitrogen for 5 min in a Schlenk tube. The solution was transferred to a 45 mL stainless steel reactor (PARR) previously purged with vacuum-nitrogen. The reaction vessel was pressurized with H_2 at 650 psi (45 bar), subsequently it was immersed in an oil bath with stir and warmed at 120 °C during 24 h. At the end of this time, the reactor was cooled and the gas was liberated. The solution was analyzed by GC–MS and after concentrated and purified by column chromatography. Characterization is similar to those described in Section 4.2.

Acknowledgements

This work was supported by CONACyT (166350) and DGAPA–UNAM (PAPIIT IN203209).

Supplementary data

Supplementary data related to this article can be found online at doi:10.1016/j.tet.2012.01.038.

References and notes

1. For a general review, see: Sewald, N.; Jakubke, H. D. *Peptides: Chemistry and Biology*; Wiley-VCH: Weinheim, 2002.
2. (a) Cupido, T.; Tulla-Puche, J.; Spengler, J.; Alberico, F. *Curr. Opin. Drug Discovery Dev.* **2007**, *10*, 768; (b) Bode, J. W. *Curr. Opin. Drug Discovery Dev.* **2006**, *9*, 765.
3. (a) Roenn, R.; Lampa, A.; Peterson, S. D.; Gossas, T.; Aakerblom, E.; Danielson, U. H.; Karlen, A.; Sandstroem, A. *Bioorg. Med. Chem.* **2008**, *16*, 2955; (b) Green, T. W.; Wuts, P. G. M. In *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley: New York, NY, 1999.
4. For a review of amide synthesis, see: (a) Beckwith, A. L. J.; Zabicky, J. In *The Chemistry of Amides*; Wiley: New York, NY, 1970; (b) Valeur, E.; Bradley, M. *Chem. Soc. Rev.* **2009**, *38*, 606.
5. (a) Molander, G.; Raushel, J.; Ellis, N. M. *J. Org. Chem.* **2010**, *75*, 4304; (b) Baum, J. C.; Milne, J. E.; Murry, J. A.; Thiel, O. R. *J. Org. Chem.* **2009**, *74*, 2207.
6. (a) Owston, N. A.; Parker, A. J.; Williams, J. M. J. *Org. Lett.* **2007**, *9*, 3599 and references cited therein; (b) Ramon, R. S.; Bosson, J.; Díez-Gonzalez, S.; Marion, N.; Nolan, S. P. *J. Org. Chem.* **2010**, *75*, 1197; (c) Fujiwara, H.; Ogasawara, Y.; Yamaguchi, K.; Mizuno, N. *Angew. Chem., Int. Ed.* **2007**, *46*, 5202; (d) Li, J. T.; Meng, X. T.; Zhai, X. L. *Ultrason. Sonochem.* **2009**, *16*, 590; (e) Allen, C. L.; Burel, C.; Williams, J. M. J. *Tetrahedron Lett.* **2010**, *51*, 2724; (f) Yamamoto, Y.; Hasegawa, H.; Yamataca, H. *J. Org. Chem.* **2011**, *76*, 4652.
7. Murahashi, S.-I.; Takeshi, N.; Saito, E. *J. Am. Chem. Soc.* **1986**, *108*, 7846.
8. Cobley, C. J.; Van en Heuvel, M.; Abbadi, A.; de Vries, J. G. *Tetrahedron Lett.* **2000**, *41*, 2467.
9. Allen, C. L.; Lapkin, A. A.; Williams, J. M. L. *Tetrahedron Lett.* **2009**, *50*, 4262.
10. Jiang, H.; Liu, B.; Li, Y.; Wong, A.; Huang, H. *Org. Lett.* **2011**, *13*, 1028.
11. (a) Li, J.; Xu, F.; Zhang, Y.; Shen, Q. *J. Org. Chem.* **2007**, *72*, 4536; (b) Yoo, W.-J.; Li, C.-J. *J. Am. Chem. Soc.* **2006**, *128*, 13064.
12. (a) Gunanathan, C.; Ben-David, Y.; Milstein, D. *Science* **2007**, *317*, 790; (b) Ghosh, S. C.; Muthaiah, S.; Zhang, Y.; Xu, X.; Hong, S. H. *Adv. Synth. Catal.* **2009**, *351*, 2643.
13. Chen, Z.-W.; Jiang, H.-F.; Pan, X.-P.; He, Z.-J. *Tetrahedron* **2011**, *67*, 5920.
14. For selected examples, see: (a) Jana, U.; Maiti, S.; Biswas, S. *Tetrahedron Lett.* **2008**, *49*, 858; (b) Quin, H.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 409.
15. (a) Song, W.; Ma, L.; Hu, L. *Synth. Commun.* **2011**, *41*, 3186 and references therein; (b) Das, B.; Redi, P. P.; Sudhakar, C.; Lingaiah, M. *Tetrahedron Lett.* **2011**, *52*, 3521.
16. For recent reviews, see: (a) Dobereiner, G. E.; Crabtree, R. H. *Chem. Rev.* **2010**, *110*, 681; (b) Guillena, G.; Ramón, D. J.; Yus, M. *Chem. Rev.* **2010**, *110*, 1611.
17. (a) Liu, C.; Liao, S.; Feng, S.; Sun, Q.; Yu, X.; Xu, Q. *J. Org. Chem.* **2011**, *76*, 57 and references therein; (b) Crabtree, R. H. *Organometallics* **2011**, *30*, 17; (c) Fujita, K.-I.; Komatsubara, A.; Yamaguchi, R. *Tetrahedron* **2009**, *65*, 3624.
18. (a) Dubé, D.; Scholte, A. A. *Tetrahedron Lett.* **1999**, *40*, 2295; (b) Alexander, M. D.; Anderson, R. E.; Sisko, J.; Weinreb, S. M. *J. Org. Chem.* **1990**, *55*, 2563; (c) Auerbach, J.; Zamore, M.; Weinreb, S. M. *J. Org. Chem.* **1976**, *41*, 725.
19. (a) Fache, F.; Jaquot, L.; Lemaire, M. *Tetrahedron Lett.* **1994**, *35*, 3313; (b) Examples either with Et_3SiH-trifluoroacetic acid (TFA) or Pd/C-TFA, see: ref. 18c.
20. One example has been described with the heterogeneous catalyst Au/Co_3O_4, see: Hamasaki, A.; Liu, X.; Tokunaga, M. *Chem. Lett.* **2008**, *37*, 1292.
21. (a) Gómez, R. M.; Sharma, P.; Arias, J. L.; Pérez-Flores, J.; Velasco, L.; Cabrera, A. *J. Mol. Catal. A: Chem.* **2001**, *170*, 271; (b) Cabrera, A.; Sharma, P.; Arias, J. L.; Velasco, J. L.; Pérez-Flores, J.; Gómez, R. M. *J. Mol. Catal. A: Chem.* **2004**, *212*, 19.
22. Unfortunately when trifluoroacetamide and phtalimide were reacted with *p*-*tert*-butyl benzaldehyde, no corresponding products were detected.
23. McNeill, E. A.; Scholer, F. R. *J. Am. Chem. Soc.* **1977**, *99*, 6243.
24. Kaesz, H. D.; Saillant, R. B. *Chem. Rev.* **1972**, *72*, 231.
25. When the crude reaction products were analyzed by GC–MS, no reduction of aldehyde or ketone to alcohol was observed.
26. Insoluble phosphine oxides or stibine oxides were not isolated as possible byproducts during the condensation. The role of water with $Co_2(CO)_8$ have not been studied in this paper in details, but some authors have proposed that $Co_2(CO)_8/H_2O$ generates cobalt-hydrido specie $HCo(CO)_4$. See examples: (a) Yadav, J. S.; Reddy, B. V. S.; Satheesh, G.; Rao, K. R. *Chem. Lett.* **2005**, *34*, 340; (b) Lee, H.-Y.; An, M. *Tetrahedron Lett.* **2003**, *44*, 2775.
27. De Ketelare, R. F.; Delbeke, F. T.; van der Kelen, G. P. *J. Organomet. Chem.* **1971**, *30*, 365.
28. Gowda, R. R.; Chakraborty, D. *Eur. J. Org. Chem.* **2011**, 2226.
29. Wang, T. U.S. Patent WO2011019405, 2011.
30. Nomura, R.; Nakano, T.; Yamada, Y.; Matsuda, H. *J. Org. Chem.* **1991**, *56*, 4076.
31. Molander, G. A.; Hiebel, M.-A. *Org. Lett.* **2010**, *12*, 4876.
32. Naik, S.; Bhattacharjya, G.; Talukdar, B.; Patel, B. K. *Eur. J. Org. Chem.* **2004**, 1254.
33. Dolezal, R.; Waisser, K.; Petrliková, E.; Kunes, J.; Kubicová, L.; Machácek, M.; Kaustová, J.; Dahse, H. M. *Arch. Pharm. Chem. Life Sci.* **2009**, *342*, 113.