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Synthesis of amides from imines using Et_3SiH/Zn system

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A simple and efficient approach for the synthesis of amides by the reaction of imines and acyl chlorides in the presence of Et_3SiH/Zn system in THF at ambient temperature is reported. Mild reaction conditions, good yields of products, short reaction time and operational simplicity are the advantages of this procedure. Copyright © 2012 John Wiley & Sons, Ltd.

Keywords: amide; imine; triethylsilane; reduction; fentanyl

Introduction

Amides are a very important class of organic compounds, with a wide range of applications. The amide bond appears as an important structural component in peptides, polymers, and many natural products and pharmaceuticals.[1–4] Various amides are biologically active and show antifungal, antihistamine, anthelmintic and antibacterial properties.[5–8] Because of their obvious importance, several methods have been described for the synthesis of amides.[9–17]

However, the majority of amide bond syntheses involve the use of stoichiometric amounts of coupling reagents, making them generally expensive and wasteful procedures.[18] Many of these methods have some disadvantages, such as the use of toxic metals, strong Lewis acids, expensive reagents, low yield and drastic reaction conditions. These difficulties have encouraged efforts towards the identification and development of more atom-efficient, catalytic methods for amide bond formation, as evidenced by the increasing number of publications in this area in recent years.[9,19–23]

The hydrosilylation of imines, in which the Si-H bond is added across the C=N bond, is an attractive alternative approach for the hydrogenation of imines as it is experimentally simple, does not require high pressure or temperature, and makes use of readily available silanes. Many transition metal complexes with metals, including Ru,[24] Rh,[25] Ti,[26] Ir,[27] Cu,[28] and Zn,[29] have been used as catalysts for imine hydrosilylation.

Although, hydrosilylation of imines to amines in the presence of transition metal-based catalysts has been reported as a synthetic strategy over the years,[24–29] the synthesis of amides via transition-metal catalyzed hydrosilylation of imines has not yet been reported. Therefore, we sought to develop a new, simple and straightforward method for amide formation from imines using an Et_3SiH/Zn system. The use of zinc is of great interest, owing to its abundance and biological relevance.

Experimental

The chemicals used in this work were obtained from Fluka and Merck and were used without purification. Zinc dust has been activated sufficiently by ethylene dibromide (EDB) in THF.[30] Melting points were measured on a Buchi B-545 apparatus. ^{1}H NMR spectra were recorded on a Bruker-DRX 500 Avance spectrometer at 500.13 MHz. IR spectra were recorded using a Shimadzu FT-IR-8300 spectrophotometer. Mass spectra were recorded on a JEOL MAT312 mass spectrometer operating at an ionization potential of 70 eV. Elemental analyses were performed using a Heracus CHN-O-Rapid analyzer.

General Procedure for the Preparation of Amide 3

A mixture of imine (1 mmol), acyl chloride (2 mmol), Et_3SiH (4 mmol) and zinc dust with chemically activated surface (1.2 mmol) in THF (5 ml) was stirred at room temperature for 30 min. After completion of the reaction, progress of reaction was m\onitored using TLC (eluent:EtOAc/petroleum ether, 1:3), the reaction mixture was filtered, and 20 ml H_2O was added to the filtrate, which was extracted with CH_2Cl_2 (3×5 ml). The organic layer was dried over anhydrous $MgSO_4$ and concentrated by rotary evaporation. The residue was purified by flash column chromatography (EtOAc/petroleum ether) to afford the pure product.

The amide products **3a**, **3c**, **3g** and **3k** are known compounds and were characterized by ^{1}H NMR spectroscopic data and their melting points, which agreed with reported values.[31,32]

N-Benzyl-*N*-phenylpropionamide (**3b**)

Cream oil;[32] IR (KBr): 3032, 2872, 1639, 1586, 806. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29 (m, 8H, H-Ar), 7.01 (d, $J = 6.9$ Hz, 2H, H-Ar), 4.92 (s, 2H, NCH_2), 2.12 (q, $J = 7.3$ Hz, 2H, CH_2), 1.11 (t, $J = 7.3$ Hz, 3H, Me). ^{13}C NMR (125 MHz, $CDCl_3$): δ 10.1 (*Me*), 28.2 (*CH_2*-CO), 53.4 (CH_2N), 127.7 (CH), 128.3 (CH), 128.7 (CH), 128.8 (CH), 129.2 (CH), 129.9 (CH), 138.1 (C_{ipso}) and 142.9 (C-N), 174.4 (CO). MS (E.I.) (70 eV): *m/z* (%) 239 (M^+, 30), 182 (50), 104 (12), 91 (45), 77 (12),

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57 (5). Anal. Calcd for $C_{16}H_{17}NO$: C, 80.30; H, 7.16; N, 5.85. Found: C, 80.21; H, 7.11; N, 5.78.

N-Benzyl-*N*-(4-chlorophenyl)propionamide (**3d**)

White powder; m.p. 112–113°C. IR (KBr): 3011, 2927, 1649, 1580, 828. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25 (m, 5H, H-Ar), 7.12 (d, J = 2.7 Hz, 2H, H-Ar), 6.93 (d, J = 8.1 Hz, 2H, H-Ar), 4.89 (s, 2H, NCH_2), 2.01 (q, J = 7.4 Hz, 2H, CH_2), 1.10 (t, J = 7.4 Hz, 3H, Me). ^{13}C NMR (125 MHz, $CDCl_3$): δ 10.2 (Me), 28.4 (*CH_2*-CO), 53.1 (CH_2N), 127.9 (CH), 128.8 (CH), 129.2 (CH), 130.1 (CH), 130.2 (CH), 137.6 (C_{ipso}), 141.7 (C-Cl) 142.9 (C-N), 171.5 (CO). MS (E.I.) (70 eV): *m/z* (%) 273 (M^+, 43), 216 (27), 111 (8), 91 (100), 77 (5). Anal. Calcd for $C_{16}H_{16}ClNO$: C, 70.20; H, 5.89; N, 5.12. Found: C, 70.09; H, 5.19; N, 5.06.

N-(4-Methoxybenzyl)-*N*-*p*-tolylacetamide (**3e**)

Cream powder; m.p. 102–104°C. IR (KBr): 3064, 2922, 1633, 1521, 814.^{1}H NMR (500 MHz, $CDCl_3$): δ 7.14 (d, J = 8.4 Hz, 4H, H-Ar), 6.86 (d, J = 8.1 Hz, 2H, H-Ar), 6.81 (d, J = 8.1 Hz, 2H, H-Ar), 4.82 (s, 2H, NCH_2), 3.81 (s, 3H, OMe), 2.37 (s, 3H, Me), 1.88 (s, 3H, Me). ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.5 (*Me*-Ar), 28.2 (*Me*-CO), 52.7 (CH_2N), 55.6 (OMe), 114.1 (CH), 128.6 (CH), 129.2 (CH), 130.5 (CH), 133.6 (*C*-Me), 138.1 (C_{ipso}), 140.3 (C-N), 159.2 (*C*-OMe), 174.2 (CO). MS (E.I.) (70 eV): *m/z* (%) 269 (M^+, 25), 226 (5), 162 (5), 121 (100). Anal. Calcd for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.88; H, 7.18; N, 5.11.

N-(4-Methoxybenzyl)-*N*-*p*-tolylpropionamide (**3f**)

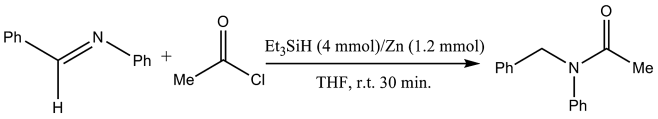
Yellow light powder; m.p. 128–129°C. IR (KBr): 3032, 2924, 1662, 1508, 1028, 817, 740.^{1}H NMR (500 MHz, $CDCl_3$): δ 7.14 (d, J = 8.3 Hz, 4H, H-Ar), 7.85 (d, J = 8.2 Hz, 2H, H-Ar), 6.8 (d, J = 8.2 Hz, 2H, H-Ar), 4.82 (s, 2H, NCH_2), 3.81 (s, 3H, OMe), 2.37 (s, 3H, Me), 2.08 (q, J = 7.4 Hz, 2H, CH_2), 1.1 (t, J = 7.4 Hz, 3H, Me). ^{13}C NMR (125 MHz, $CDCl_3$): δ 10.1 (*Me*-CH_2), 21.1 (*Me*-Ar), 28.4 (*CH_2*-CO), 52.9 (CH_2N), 55.9 (OMe), 114.0 (CH), 128.3 (CH), 129.0 (CH), 130.4 (CH), 133.5 (*C*-Me), 137.2 (C_{ipso}), 139.9 (C-N) 159.0 (*C*-OMe), 174.4 (CO). MS (E.I.) (70 eV): *m/z* (%) 283 (M^+, 25), 226 (5), 176 (5), 121 (100), 91 (8), 77 (8). Anal. Calcd for $C_{18}H_{21}NO_2$: C, 76.29; H, 7.47; N, 4.94. Found: C, 76.17; H, 7.38; N, 5.07.

N-(4-Methoxybenzyl)-*N*-phenylpropionamide (**3h**)

White powder; m.p. 98–99°C. IR (KBr): 3061, 2935, 1662, 1510, 1031, 842, 777. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34 (m, 3H, H-Ar), 7.12 (d, J = 2.7 Hz, 2H, H-Ar), 6.98 (d, J = 8.5 Hz, 2H, H-Ar), 6.81 (d, J = 8.5 Hz, 2H, H-Ar), 4.85 (s, 2H, NCH_2), 3.80 (s, 3H, OMe), 2.08 (q, J = 7.3 Hz, 2H, CH_2), 1.09 (t, J = 7.3 Hz, 3H, Me). ^{13}C NMR (125 MHz, $CDCl_3$): δ 10.1 (*Me*-CH_2), 28.2 (*CH_2*-CO), 52.7 (CH_2N), 55.6 (OMe), 114.1 (CH), 128.2 (CH), 128.9 (CH), 129.8 (CH), 130.3 (CH), 136.6 (C_{ipso}), 142.8 (C-N) 159.2 (*C*-OMe), 174.1 (CO). MS (E.I.) (70 eV): *m/z* (%) 269 (M^+, 18), 212 (5), 121 (100), 104 (5), 91 (6), 77 (8). Anal. Calcd for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.75; H, 7.04; N, 5.15.

N-(4-Chlorobenzyl)-*N*-*p*-tolylacetamide (**3i**)

Cream powder; m.p. 173–175°C. IR (KBr): 3001, 2858, 1658, 1512, 825, 802. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25 (d, J = 2.6 Hz, 2H, H-Ar), 7.16 (m, 4H, H-Ar), 6.87 (d, J = 5.8 Hz, 2H, H-Ar), 4.85 (s, 2H, NCH_2), 2.38 (s, 3H, Me), 1.9 (s, 3H, Me). ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.2 (*Me*-Ar), 28.4 (*Me*-CO), 52.6 (CH_2N), 127.3 (CH), 128.8 (CH), 129.4 (CH), 130.2 (CH), 133.1 (*C*-Me), 136.9 (C_{ipso}), 141.8 (C-Cl), 142.1 (C-N)), 172.4 (CO). MS (E.I.) (70 eV): *m/z* (%) 273 (M^+, 85), 231 (100), 180 (3), 162 (3), 125 (85), 91 (15), 77 (8), 43 (23). Anal. Calcd for $C_{16}H_{16}ClNO$: C, 70.20; H, 5.89; N, 5.12. Found: C, 70.28; H, 5.81; N, 5.23.



Scheme 1. Model reaction and conditions.

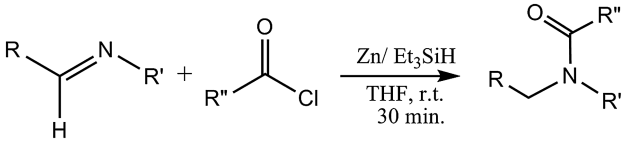
N-(4-Chlorobenzyl)-*N*-*p*-tolylpropionamide (**3j**)

White powder; m.p. 196-198°C. IR (KBr): 3032, 2935, 1660, 1390, 879, 829. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26 (d, J = 2.6 Hz, 2H, H-Ar), 7.17 (m, 4H, H-Ar), 4.84 (s, 2H, NCH_2), 2.17 (s, 3H, Me), 2.01 (q, J = 7.4 Hz, 2H, CH_2), 1.09 (t, J = 7.4 Hz, 3H, Me). ^{13}C NMR (125 MHz, $CDCl_3$): δ 10.4 (*Me*-CH_2), 21.5 (*Me*-Ar), 28.4 (*CH_2*-CO), 53.0 (CH_2N), 127.5 (CH), 128.2 (CH), 129.7 (CH), 130.4 (CH), 133.0 (*C*-Me), 136.6 (C_{ipso}), 141.9 (C-Cl) 142.5 (C-N)), 172.9 (CO). MS (E.I.) (70 eV): *m/z* (%) 287 (M^+, 50), 231 (100), 196 (15), 125 (59), 91 (13), 57 (4). Anal. Calcd for $C_{17}H_{18}ClNO$: C, 70.95; H, 6.30; N, 4.87. Found: C, 70.82; H, 6.21; N, 4.78.

N-(4-Chlorobenzyl)-*N*-(4-chlorophenyl)propionamide (**3l**)

White powder; m.p. 115–116°C. IR (KBr): 3026, 2873, 1662, 1512, 827, 804. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.11 (m, 6H, H-Ar), 6.87 (d, J = 8.0 Hz, 2H, H-Ar), 4.85 (s, 2H, NCH_2), 2.10 (q, J = 7.4 Hz, 2H, CH_2), 1.1 (t, J = 7.4 Hz, 3H, Me). ^{13}C NMR (125 MHz, $CDCl_3$): δ 10.1 (Me), 28.2 (*CH_2*-CO), 52.7 (CH_2N), 127.9, 129.1, 130.4, 130.6, 136.3 (C_{ipso}), 141.0 (C-Cl), 141.6 (C-Cl), 142.2 (C-N)), 174.0 (CO). MS (E.I.)

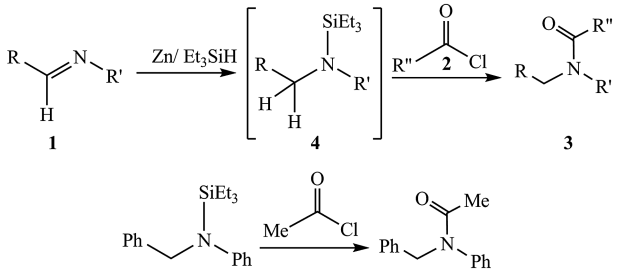
Table 1. Synthesis of amide **3**



1a-i **2a,b** **3a-o**

Product **3**	R	R′	R″	Yield (%)[a]
a	C_6H_5	C_6H_5	Me	85
b	C_6H_5	C_6H_5	Et	81
c	C_6H_5	4-Cl-C_6H_4	Me	82
d	C_6H_5	4-Cl-C_6H_4	Et	80
e	4-MeO-C_6H_4	4-Me-C_6H_4	Me	76
f	4-MeO-C_6H_4	4-Me-C_6H_4	Et	73
g	4-MeO-C_6H_4	C_6H_5	Me	80
h	4-MeO-C_6H_4	C_6H_5	Et	76
i	4-Me-C_6H_4	4-Cl-C_6H_4	Me	78
j	4-Me-C_6H_4	4-Cl-C_6H_4	Et	77
k	4-Cl-C_6H_4	4-Cl-C_6H_4	Me	84
l	4-Cl-C_6H_4	4-Cl-C_6H_4	Et	80
m	4-Cl-C_6H_4	4-Me-C_6H_4	Me	76
n	4-Me-C_6H_4	4-Me-C_6H_4	Me	72
o	4-Me-C_6H_4	4-Me-C_6H_4	Et	70
p	C_6H_5	C_6H_{11}	Me	76
q	C_6H_5	$CH_2CH(Me)_2$	Me	81

[a]Isolated yield.



Scheme 2. Proposed mechanism.

(70 eV): *m/z* (%) 307 (M^+, 50), 251 (100), 216 (11), 125 (75), 111 (5), 57 (20). Anal. Calcd for $C_{16}H_{15}Cl_2NO$: C, 62.35; H, 4.91; N, 4.54. Found: C, 62.42; H, 4.96; N, 4.47.

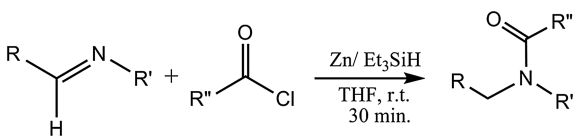
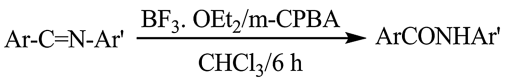
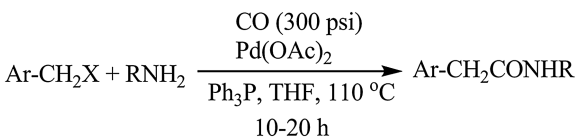
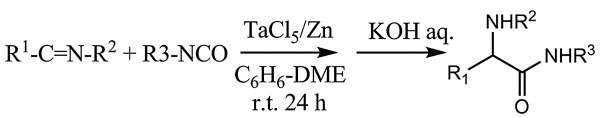
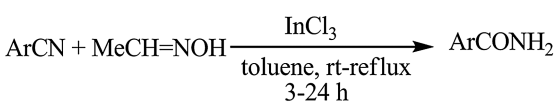
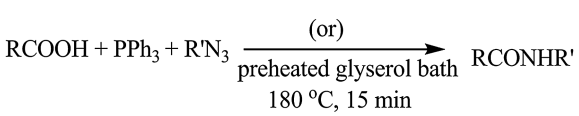
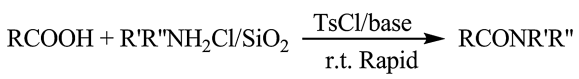
N-(4-Chlorophenyl)-*N*-(4-methylbenzyl)acetamide (**3m**)

White powder; m.p. 153–154°C. IR (KBr): 3001, 2858, 1689, 1512, 1458, 904. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31 (d, J = 8.6 Hz, 2H, H-Ar), δ 7.09 (bs, 4H, H–Ar), 6.94 (d, J = 8.6 Hz, 2H, H-Ar), 4.85 (s, 2H, NCH_2), 2.35 (s, 3H, Me), 1.9 (s, 3H, Me). ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.5 (*Me*-Ar), 27.9 (*Me*-CO), 52.8 (CH_2N), 128.3 (CH), 128.6 (CH), 129.3 (CH), 130.1 (CH), 133.3 (*C*-Me), 137.3 (C_{ipso}), 141.1 (C-Cl) 142.8 (C-N)), 170.6 (CO). MS (E.I.) (70 eV): *m/z* (%) 273 (M^+, 35), 238 (2), 230 (27), 105 (100), 91 (4), 77 (12), 43 (10). Anal. Calcd for $C_{16}H_{16}ClNO$: C, 70.20; H, 5.89; N, 5.12. Found: C, 70.09; H, 5.95; N, 5.01.

N-(4-Methylbenzyl)-*N*-*p*-tolylacetamide (**3n**)

White powder; m.p. 188–190°C. IR (KBr): 3032, 2862, 1660, 1537, 916, 794. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.11 (m, 6H, H-Ar), 6.9 (d, J = 8.2 Hz, 2H, H-Ar), 4.85 (s, 2H, NCH_2), 2.37 (s, 3H, Me), 2.34 (s, 3H, Me), 1.54 (s, 3H, Me). ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.4 (*Me*-Ar), 23.1 (*Me*-Ar), 28.2 (*Me*-CO), 52.7 (CH_2N), 127.0 (CH), 128.6 (CH), 130.4 (CH), 130.5 (CH), 133.6 (*C*-Me), 134.2 (*C*-Me), 138.1 (C_{ipso}), 141.5 (C-N)), 174.2 (CO). MS (E.I.) (70 eV): *m/z* (%) 253 (M^+, 62), 238 (2), 210 (48), 119 (8), 162 (8), 105 (100). Anal. Calcd for $C_{17}H_{19}NO$: C, 80.60; H, 7.56; N, 5.53. Found: C, 80.53; H, 7.50; N, 5.45.

Table 2. Comparison of efficiency of various methods in the synthesis of amides

Method	Yield (%)	Ref.
	70–85	This work
	39–91	[21]
	23–97	[15]
	59–93	[34]
	73–99	[13]
	67-88	[17]
	70–90	[35]

N-(4-Methylbenzyl)-*N*-*p*-tolylpropionamide (**3o**)

Cream powder; m.p. 218–219°C. IR (KBr): 3018, 2927, 1654, 1511, 910, 808. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.11 (m, 6H, H-Ar), 6.87 (d, J = 8.0 Hz, 2H, H-Ar), 4.84 (s, 2H, NCH_2), 2.37 (s, 3H, Me), 2.34 (s, 3H, Me), 2.10 (q, J = 7.4 Hz, 2H, CH_2), 1.11 (t, J = 7.4 Hz, 3H, Me). ^{13}C NMR (125 MHz, $CDCl_3$): δ 10.1 (*Me*-CH_2), 21.5 (*Me*-Ar), 22.6 (*Me*-Ar), 28.1 (*Me*-CO), 52.3 (CH_2N), 127.9 (CH), 128.6 (CH), 130.0 (CH), 130.2 (CH), 133.8 (*C*-Me), 134.1 (*C*-Me), 137.5 (C_{ipso}), 141.3 (C-N), 174.5 (CO). MS (E.I.) (70 eV): *m/z* (%) 267 (M^+, 63), 210 (50), 176 (5), 163 (5), 120 (6), 105 (100), 91 (8). Anal. Calcd for $C_{18}H_{21}NO$: C, 80.86; H, 7.92; N, 5.24. Found: C, 80.94; H, 7.86; N, 5.34.

N-Benzyl-*N*-cyclohexylacetamide (**3p**)

Cream oil. IR (KBr): 3013, 2918, 1661, 1509, 915. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.22 (m, 5H, H–Ar), 4.82 (s, 2H, NCH_2), 3.02 (m, 1H, NCH), 2.31 (s, 3H, Me), 0.94–1.02 (m, 10H, 5CH_2 of cyclohexyl). ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.1, 23.2 and 24,5 (cyclohexyl), 28.4 (Me), 48.5 (CHN), 52.0 (CH_2N), 127.6 (CH), 128.9 (CH), 136.4 (C_{ipso}), 141.2 (C-N), 171.4 (CO). MS (E.I.) (70 eV): *m/z* (%) 231 (M^+, 55), 188 (35), 140 (15), 91 (100). Anal. Calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.15; N, 6.05. Found: C, 77.82; H, 9.07; N, 6.11.

N-Benzyl-*N*-isobutylacetamide (**3q**)

Cream oil. IR (KBr): 3021, 2932, 1659, 1513, 907. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.23 (m, 5H, H-Ar), 4.80 (s, 2H, NCH_2), 2.89 (d, J = 7.1 Hz, 2H, CH_2), 2.31 (s, 3H, Me), 2.11 (m, 1H, CH), 1.02 (d, J = 6.9 Hz, 6H, 2Me). ^{13}C NMR (125 MHz, $CDCl_3$): δ 19.8 (*Me*-CH), 28.1 (*Me*-CO), 28.9 (CH), 52.1 (CH_2N), 53.8 (CH-*CH_2*-N), 128.1 (CH), 130.2 (CH), 137.1 (C_{ipso}), 141.0 (C-N), 172.1 (CO). MS (E.I.) (70 eV): *m/z* (%) 205 (M^+, 48), 162 (15), 148 (95), 91 (100). Anal. Calcd for $C_{13}H_{19}NO$: C, 76.06; H, 9.33; N, 6.82. Found: C, 75.95; H, 9.41; N, 6.76.

Results and Discussion

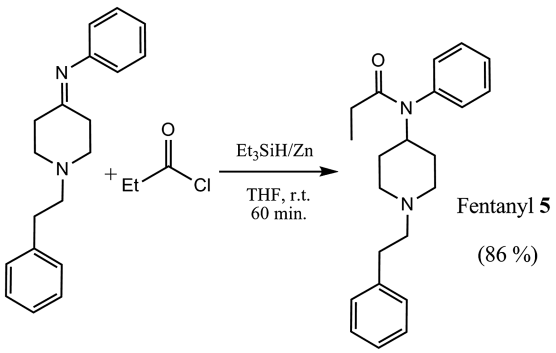
Initially, the reaction of *N*-benzylideneaniline **1a**, acetyl chloride **2a** and Et_3SiH as a simple model substrate was investigated in the presence of zinc dust as an inexpensive and readily available catalyst in THF at room temprature using different quantities of reagents. The best result was obtained with a 1:2:4:1.2 ratio of *N*-benzylideneaniline, acetyl chloride, Et_3SiH and Zn (Scheme 1). To study the effect of amount of Zn, the reaction was carried out at different amounts of Zn. It was found that using a lower amount of catalyst resulted in lower yields, while a higher amount of catalyst did not affect reaction times and yields. When this reaction was carried out without Zn the yield of the expected product was only trace.

To investigate the generality and versatility of this method, the reaction was extended to various imines **1a–j** and acyl chlorides **2a**,**b**. As is clear from Table 1, the reactions proceeded rapidly and cleanly at room temperature, and the amides **3a–q** were obtained in good yields. The aromatic imines carrying both electron-withdrawing and electron-releasing substituents and imines containing aliphatic group were also converted to their corresponding amides in good yields (Table 1).

Compound **3** apparently results from the initial reduction of imine **1** by Et_3SiH/Zn as reducing agent[33] to yield *N*-silylamine **4**, which reacts with acyl chloride **2** to afford the corresponding product (Scheme 2). To clarify the proposed mechanism, first, *N*-benzyl-*N*-(triethylsilyl)benzenamine **4a** was synthesized. Subsequently, reaction of **4a** with acetyl chloride afforded the corresponding *N*-benzyl-*N*-phenylacetamide **3a** in 84% yield (Scheme 2).

Table 2 compares efficiency of the present method with efficiency of some other methods in the synthesis of amides. It is clear from Table 2 that our method is simpler and more efficient for the synthesis of amide derivatives.

Finally, to further explore the potential of this method, we considered the synthesis of fentanyl **5** (Scheme 3) because of its high potency and generally favorable pharmacological properties. Fentanyl, or 1-(2-phenylethyl)-4-(*N*-propionylphenylamino)piperidine, is a well-known and clinically widely used narcotic analgesic, about 50–100 times more potent than morphine in humans. Fentanyl is widely used in anesthesiology and reanimatology as a means of premedication in surgery, initial narcosis, postoperative analgesic treatment, pain relief in cases of myocardial infarction and chronic heart decease in oncological patients, and neuroleptanalgesic treatment in combination with neuroleptic drugs such as droperidol.[36–38]



Scheme 3. Synthesis of fentanyl **5**.

Conclusion

We have reported for the first time a new and efficient method for amide bond formation via the reaction of imines and acyl chlorides in the presence of an Et_3SiH/Zn system at room temperature. We believe this method will find useful applications in the growth of amide bond formation chemistry.

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