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A new method for the synthesis of amides from imines

Mohammad Ghaffarzadeh *, Somaye Shahrivari Joghan, Fereshteh Faraji

Chemistry and Chemical Engineering Research Center of Iran (CCERCI), PO Box 14335-186, Tehran, Iran

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ABSTRACT

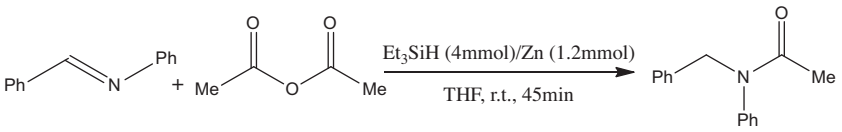
An efficient and straightforward method for the synthesis of amides by the reaction of imines and anhydrides in the presence of Et_3SiH/Zn is reported. Mild reaction conditions, good yields of products, short reaction times, and operational simplicity are advantages of this procedure.

The formation of amides has attracted considerable interest due to their importance in organic and bioorganic chemistry, their value as intermediates in organic synthesis and a wide range of applications in the chemical industry. The amide bond is an important structural component of peptides, polymers, and many natural products and pharmaceuticals.[1–4] Numerous amides are biologically active and show antifungal, antihistamine, anthelmintic, and antibacterial properties.[5–8] Several methods have been described for the synthesis of amides; these include (i) reaction of an amine with a carboxylic acid, carboxylic acid derivatives, aldehydes, or alcohols,[9–12] (ii) hydration of nitriles into primary amides,[13] (iii) coupling of amines with nitriles,[9] (iv) coupling of nitriles with alcohols (Ritter reaction),[14] (v) rearrangement of aldoximes into primary amides,[9,11] (vi) Beckmann rearrangement of ketoximes into secondary amides,[9] (vii) coupling of aldoximes and amines,[9] (viii) palladium-catalyzed aminocarbonylation of aryl halides, vinyl halides, or benzyl halides,[9,15] (ix) N-arylation and N-alkenylation of amides,[9] (x) rearrangement of ketones into amides with $TMSN_3$,[16] (xi) reaction of carboxylic acids with isocyanides,[17] (xii) coupling of phosphazenes with carboxylic acids,[18] and (xiii) reaction of azides and thioacids.[19]

However, the use of imines as precursors for the synthesis of amides has seldom been described. In 1988, Vasapollo and Alper reported the diacylation of Schiff bases using catalytic quantities of cobalt carbonyl and phase-transfer catalysis conditions.[20]

The oxidation of aldimines to amides using *m*-CPBA and $BF_3{\cdot}OEt_2$ was reported by Rhee and co-workers.[21] Recently, the synthesis of α-amino amides by the reaction of imines and isocyanates using $TaCl_5$/Zn was described.[22] Therefore, we sought to develop a new, simple, and straightforward method for amide formation from imines using the silicon-based reducing agent, Et_3SiH, in the presence of zinc dust.

Initially, we performed the reaction of *N*-benzylideneaniline (**1a**), acetic anhydride (**2a**) and Et_3SiH/Zn in THF at room tempera-



1a (1 mmol) **2a** (2 mmol) **3a** (80%)

Scheme 1. Model reaction.

* Corresponding author. Fax: +98 2144580762.
E-mail address: mghaffarzadeh@ccerci.ac.ir (M. Ghaffarzadeh).

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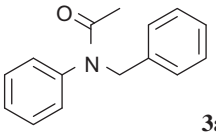
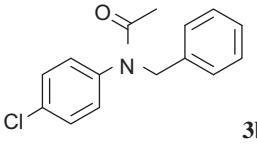
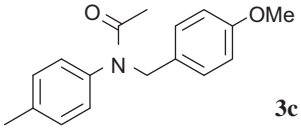
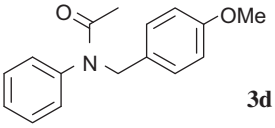
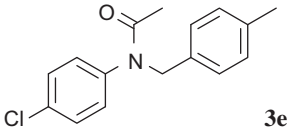
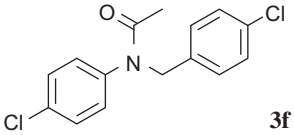
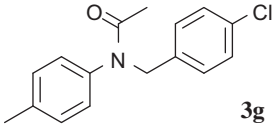
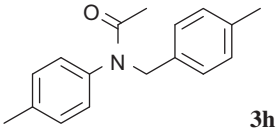
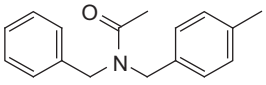
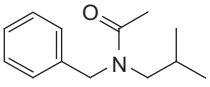
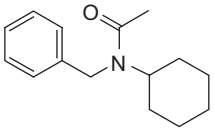
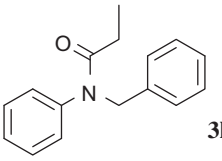
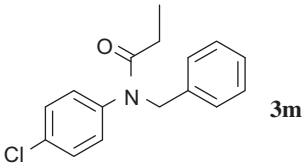
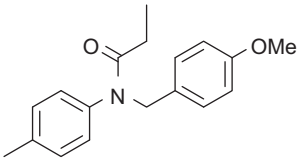
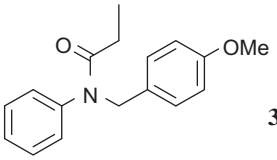
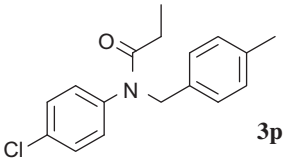
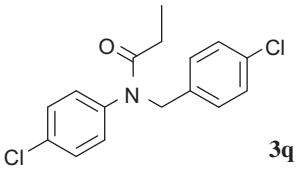
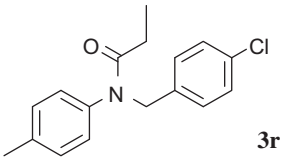
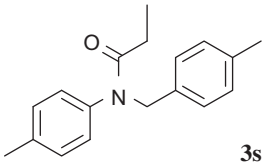
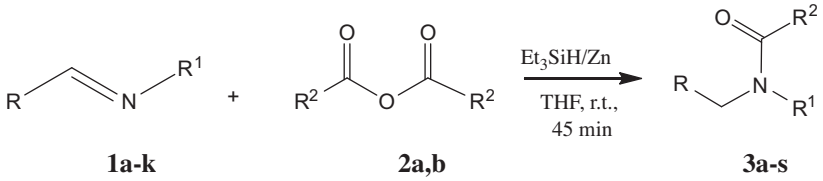
ture using different quantities of reagents. The best result was obtained with a 1:2:4:1.2 ratio of *N*-benzylideneaniline, acetic anhydride, Et_3SiH and zinc (Scheme 1). When this reaction was carried out without zinc the expected product was obtained only in trace amount.

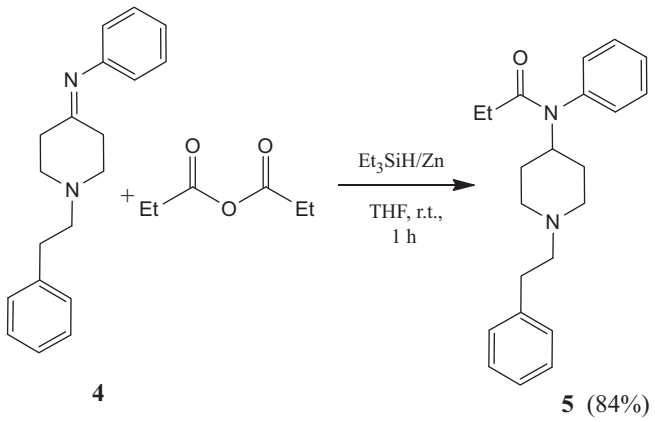
Next, the general efficiency of the method was studied for the synthesis of a variety of amides and the results are summarized in Table 1. Various imines **1a–k** reacted efficiently with anhydrides **2a,b** to afford the amides **3a–s** under similar conditions (Scheme 2). Imines possessing electron-withdrawing and electron-releasing

Table 1
Synthesis of amides **3a–s**

Product	Yield (%)	Product	Yield (%)
 **3a**	80	 **3b**	80
 **3c**	78	 **3d**	78
 **3e**	68	 **3f**	65
 **3g**	70	 **3h**	69
 **3i**	72	 **3j**	70
 **3k**	80	 **3l**	73
 **3m**	72	 **3n**	75
 **3o**	65	 **3p**	70
 **3q**	86	 **3r**	65
 **3s**	84		



Scheme 2. Synthesis of amides **3a–s**.



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

substituents were also converted into the corresponding amides in good yields (Table 1).

To explore further the potential of this method, we undertook 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 used in anesthesiology and reanimatology as a means of premedication in surgery, for initial narcosis, post-operation analgesic treatment, pain relief in cases of myocardial infarction and chronic heart disease in oncological patients, and in neuroleptanalgesic treatment in combination with neuroleptic drugs such as droperidol.[23–25]

Amides **3** apparently result from initial reduction of imine **1** by Et_3SiH/Zn to yield *N*-silylamine **6**, which reacts with anhydride **2** to afford the corresponding product (Scheme 4).

In conclusion, we have reported an efficient and novel method for amide bond formation via the reaction of imines and anhydrides in the presence of Et_3SiH/Zn at room temperature. We believe this method will find useful applications in amide chemistry.

General procedure for the preparation of amide 3

A mixture of imine (1 mmol), anhydride (2 mmol), Et_3SiH (4 mmol), and activated Zn dust (1.2 mmol) in THF (5 mL) was stirred at room temperature for 45 min (the progress of the reaction was monitored by TLC). After completion of the reaction, the mixture was filtered, and H_2O (20 mL) was added to the filtrate which was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layer was dried over anhydrous $MgSO_4$ and concentrated by rotary evaporation. The residue was purified by flash column chromatography (EtOAc/petroleum ether).

Synthesis of *N*-(1-phenethylpiperidin-4-ylidene)aniline[26] (4)

A mixture of 1-phenethylpiperidin-4-one (2 mmol), aniline (2 mmol), and a catalytic amount of *p*-TsOH (0.03 g) in toluene was stirred at reflux with the removal of H_2O using a Dean–Stark trap for 24 h. The reaction mixture was cooled and the solvent evaporated. The residue was recrystallized from *n*-hexane to afford pure product **4** (0.22 g, 80%).

Synthesis of fentanyl (5)

A mixture of **4** (1 mmol), propionic anhydride (2 mmol), Et_3SiH (4 mmol), and activated Zn dust (1.2 mmol) in THF (5 ml) was stirred at room temperature for 1 h. After completion of the reaction, the mixture was filtered, and H_2O (20 mL) was added to the filtrate which was extracted with CH_2Cl_2 (3 × 5 mL). The combined 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 fentanyl (**5**) (0.28 g, 84%). Mp 84–85 °C (Lit.[25] mp 82–83 °C). IR (KBr) (ν_{max}/cm^{-1}): 3057, 1656, 1612. MS, *m*/*z*: 336 (M^+, 5), 245 (10), 188 (120), 189 (15), 91 (80), 77 (42), 57 (100). ^{1}H NMR (500 MHz, $CDCl_3$): δ_H (ppm) 1.04 (t, *J* = 7.4 Hz, 3H), 1.48–1.58 (m, 4H), 1.95 (q, *J* = 7.4 Hz, 2H), 2.21 (m, 2H), 2.57–2.76 (m, 4H), 3.04 (m, 2H), 4.72 (m, 1H), 7.12 (m, 2H), 7.19 (m, 3H), 7.28 (m, 2H), 7.4 (m, 3H).

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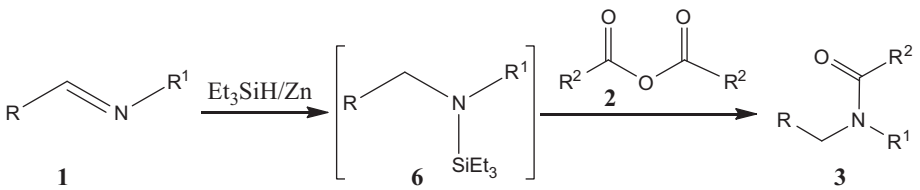

Scheme 4. Proposed mechanism.

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