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Ruthenium(III) chloride-catalyzed efficient protocol for ethyl diazoacetate insertion into the N–H bond of secondary amines

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Abstract Ruthenium(III) chloride (1 mol%) alone can catalyze the insertion of ethyl diazoacetate into N–H bonds of various structurally and electronically diverse secondary cyclic amines under solvent-free conditions to afford the corresponding glycine esters in good yields under ambient conditions. Reactions with various aliphatic primary and aromatic amines examined, however, were unsuccessful.

Keywords Ruthenium(III) chloride; Insertion; Amines; Ethyl diazoacetate; Solvent-free conditions.

Introduction

The insertion of *in situ* generated metallocarbenoid species as the catalytic active species for the transfer of a carbene moiety from a diazo source into heteroatom–H bonds [1], which are valuable synthons in the synthesis of α-amino acids, peptides, and β-lactam antibiotics [2], remains of considerable attention in organic synthesis.

The N–H insertion reaction particularly reported by *Yates* using copper bronze [3], has received much attention in the last few decades. *Saegusa et al*. [4] and *Kagan* and *Nicoud* [5] employed CuCN as a catalyst for the insertion of diazo compounds into N–H bonds. Later $Rh(OAc)_2$ and its derivatives have proved to be excellent catalysts for the insertion reaction of diazo compounds into *X*–H bonds ($X =$ heteroatom) [6]. *Simonneaux et al*. reported this reaction using ruthenium complexes [7]. *Morilla et al*. rediscovered Cu(I) homoscorpionate complex for the reaction of different amines and diazo compounds under mild conditions [8]. *Perez* and co-workers reported the $\{[HC(3,5\text{-}Me_2pz)_3]Cu(NCMe)\}BF_4$ complex catalyzed transfer of the:$CHCO_2Et$ unit from ethyl diazoacetate (*EDA*) to several saturated and unsaturated substrates with very high yields and under biphasic conditions using ionic liquid [*bmim*]-$[PF_6]$ and *n*-hexane as the reaction medium [9]. *Kantam et al*. reported the insertion of α-diazo compounds into N–H bonds of amines using $Cu(acac)_2$ immobilized in ionic liquids [10]. Very recently, an elegant procedure was developed by *Woo et al*. using iron porphyrin as catalyst for the N–H insertion reactions with *EDA* [11]. Keeping in the view of limited procedures so far for the effective insertion of ethyl diazoacetate into N–H bonds of amines, there is further scope to explore and understand the present reaction.

Another promising synthesis approach to environmentally friendly chemistry is to minimize or eliminate the use of harmful organic solvents. Organic reactions under solvent-free conditions are advantageous because of their enhanced selectivity and efficiency, ease of manipulation, cleaner product formation, and toxic or often volatile solvents are avoided [12].

Very recently, we have reported an aldol-type reaction of aldehydes with *EDA* using quaternary

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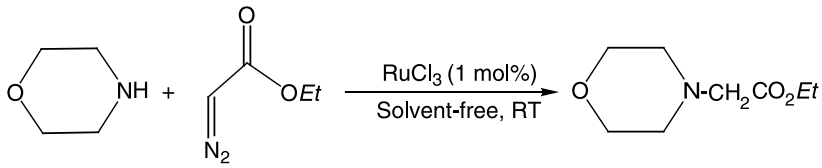
ammonium hydroxide as base [13]. During the course of our target to synthesize α-amino acids and having been interested in exploring novel synthesis protocols, particularly for carbon–carbon, carbon–heteroatom bond forming reactions [14], we undertook a study on the insertion of *EDA* into N–H bonds of various structurally and electronically divergent amines.

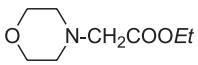
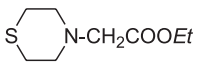
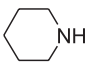
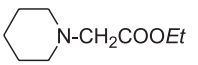
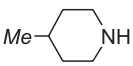
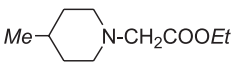
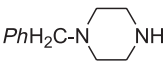
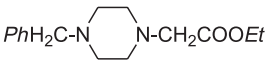
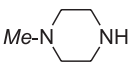
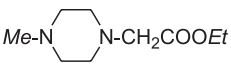
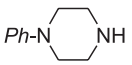
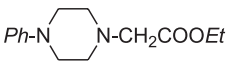
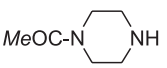
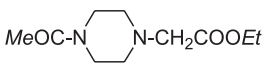
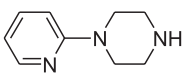
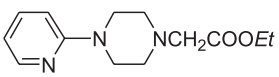
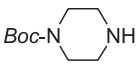
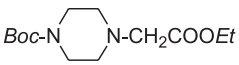
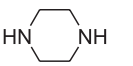
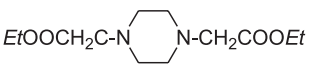
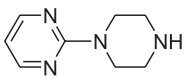
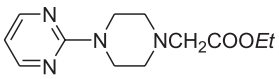
Results and discussion

Initially, we screened the catalytic activity of several reagents chosen (5 mol% as standard) such as Ru(*acac*)$_3$, Co(*acac*)$_3$, Pd(*acac*)$_2$, VO(*acac*)$_2$, Nd(NO_3)$_3$, $RhCl_3$, $RuCl_3$, Zn(O*Tf*)$_2$, $PrCl_3$, $TbCl_3$, $SmCl_3$, $FeCl_3$, and $CeCl_3 \cdot 7H_2O$ using 1 mmol *EDA* as carbene source with morpholine (1.2 mmol) under solvent-free conditions at ambient temperature. Among the reagents screened, $RuCl_3$ proved to be the best catalyst for the model reaction both in terms of yields and reaction times. To our delight, we observed the formation of the corresponding N–H insertion product in 95% yield of isolated product after 1 h (Scheme 1). The ^{1}H NMR spectroscopic analysis revealed the formation of a new signal at



Scheme 1

Table 1 $RuCl_3$-catalyzed insertion of *EDA* into funtionalized amines

Formula number	Amine	Product	Time/h	Yields/%[a,b]	Ref.
1			1.0	95	[8]
2			1.5	60	–
3			1.0	88	[11]
4			8.0	45	–
5			3.5	78	–
6			4.5	85	–
7			3.0	68	–
8			12.0	38	–
9			3.0	82	–
10			4.5	85	–
11[c]			4.5	72	[10]
12			4.5	92	–

[a] Yields refer to isolated pure products after column chromatography
[b] All new compounds were characterized by ^{1}H NMR, IR, and mass spectra
[c] 2 mmol *EDA* were used

$\delta = 3.15$ ppm for the N–CH_2 and the disappearance of N_2=CH proton of *EDA* at $\delta = 4.72$ ppm.

Further studies revealed that 1 mol% of catalyst was also efficient to carry forward the insertion process (1 mol%, 1 h, ≈95% yield). We also screened several solvents (*Et*OH, *THF*, H_2O, CH_3CN, toluene, *DCM*, *DMF*, and *DMSO*), interestingly no insertion product was observed. The optimum yields of the product were obtained when a ratio of substrate to *EDA* (1.1:1) is used. When equimolar ratios of *EDA* to amine were used trace amounts of side products, such as diethyl fumarate, diethyl maleate (due to dimerization of *EDA*), or ethyl glyoxalate azine were observed. Based on literature reports by *Simonneaux et al*. [7a, c] we took amines slightly in excess to *EDA* in order to prevent the formation of the side products [15]. The addition of *EDA* to the amine was done slowly so as to prevent the dimerization of *EDA*.

Having optimized the reaction conditions, we demonstrated the generality and scope of this method for the reaction between *EDA* and structurally divergent functionalized secondary cyclic amines and the results are summarized in Table 1. Moderate to excellent isolated yields were observed for all substrates employed. The present protocol is very clean and free from side reactions and does not require inert conditions. In the absence of the catalyst, the desired product was not formed. It is interesting to note that for entries 4 and 8, the isolated yields of the corresponding insertion products were low and required longer reaction times. Whereas in case of piperazine (1.1 equiv., entry 11), 2 mmol of *EDA* were employed by adding stepwise for the double insertion to occur. Satisfied by these results, we extended our $RuCl_3$ catalyzed protocol for various aliphatic primary and aromatic amines, such as cyclohexyl amine, *n*-butyl amine, allyl amine, aniline, and benzyl amine *etc.*, but these experiments were unsuccessful.

Based on the report by *Simonneaux et al*. [7], we presume that the active intermediate in the catalyzed ethyl diazoacetate insertion into the N–H bond is a ruthenium carbene complex. *EDA* was then added to the carbene complex which thereafter leads to the formation of the expected glycine ester.

Conclusion

In conclusion, we have preliminary demonstrated that $RuCl_3$ (1 mol%) alone is sufficient for a facile N–H insertion of ethyl diazoacetate into a wide range of secondary cyclic amines under mild conditions at ambient temperature with moderate to excellent yields under atmospheric conditions. Although this protocol offers limited applicability, it is the first example using a simple Ru salt as the catalyst for diazo N–H insertion. Further exploration of the full applicability for the *EDA* insertion into various primary aliphatic and aromatic amines using anchored ruthenium salts is currently underway.

Experimental

^{1}H NMR spectra of $CDCl_3$ solutions were recorded on Varian FT-200 MHz (Gemini) and Bruker UXNMR FT-300 MHz (Avance) instruments. The chemical shifts are reported as parts per million downfield from tetramethylsilane. Mass spectra were recorded on a VG 7070H Micro mass spectrometer. The purity of the compounds was checked by TLC on precoated SiO_2 gel (HF254, 200 mesh) aluminum plates (E. Merck) using *n*-hexane:ethyl acetate (8:2) as mobile phase and compounds were visualized by iodine vapors.

General procedure for the insertion of EDA into amines
To a stirred solution of 1.1 mmol amine and 1 mol% $RuCl_3$ was added *EDA* (1 mmol) slowly at room temperature under solvent-free conditions (Table 1). After completion of the reaction as indicated by TLC, the crude product was extracted with $2 \times 5\,cm^3$ diethyl ether. The combined products were concentrated *in vacuo* and the crude residue was purified by silica gel column chromatography to afford the corresponding pure addition product in good yields. The known compounds in Table 1 were found to be identical with respect to the published ^{1}H NMR and mass data [8, 10, 11] and novel compounds were characterized by ^{1}H NMR and mass spectral analyses.

Ethyl 2-(1,4-thiazinan-4-yl)acetate (**2**, $C_8H_{15}NO_2S$)
Oil; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.31$ (t, $J = 7.51$ Hz, 3H), 2.84 (t, $J = 4.53$ Hz, 4H), 3.18 (s, 2H), 3.38 (t, $J = 4.53$ Hz, 4H), 4.22 (q, $J = 7.55$ Hz, 2H) ppm; MS (EI): $m/z = 189$ (M^+).

Ethyl 2-(4-methylpiperidino)acetate (**4**, $C_{10}H_{19}NO_2$)
Oil; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.96$ (d, 3H), 1.23–1.28 (m, 5H), 1.26 (t, $J = 7.24$ Hz, 3H), 2.52–2.58 (m, 4H), 3.15 (s, 2H), 4.17 (q, $J = 7.03$ Hz, 2H) ppm; MS (EI): $m/z = 185$ (M^+).

Ethyl 2-(4-benzylpiperazino)acetate (**5**, $C_{15}H_{22}N_2O_2$)
Oil; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.27$ (t, $J = 6.79$ Hz, 3H), 2.37–2.58 (m, 4H), 2.87 (t, $J = 4.53$ Hz, 4H), 3.15 (s, 2H), 3.47 (s, 2H), 4.18 (q, $J = 6.79$ Hz, 2H), 7.25–7.27 (m, 5H) ppm; MS (EI): $m/z = 262$ (M^+).

Ethyl 2-(4-methylpiperazino)acetate (**6**, $C_9H_{18}N_2O_2$)
Oil; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.29$ (t, $J = 6.79$ Hz, 3H), 2.26 (s, 3H), 2.36–2.58 (m, 8H), 3.16 (s, 2H), 4.16 (q, $J = 6.79$ Hz, 2H) ppm; MS (EI): $m/z = 185$ (M^+).

Ethyl 2-(4-phenylpiperazino)acetate (**7**, $C_{14}H_{20}N_2O_2$)
Oil; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.29$ (t, $J = 6.79$ Hz, 3H), 2.73 (t, $J = 5.28$ Hz, 4H), 3.20 (t, $J = 5.28$ Hz, 4H), 3.22 (s, 2H), 4.18 (q, $J = 6.79$ Hz, 2H), 6.78–6.99 (m, 2H), 7.17–7.25 (m, 3H) ppm; MS (EI): $m/z = 248$ (M^+).

Ethyl 2-(4-acetylpiperazino)acetate (**8**, $C_{10}H_{18}N_2O_3$)
Oil; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.27$ (t, $J = 7.0$ Hz, 3H), 2.07 (s, 3H), 2.59–2.68 (m, 4H), 3.21 (s, 2H), 3.18–3.29 (m, 4H), 4.18 (q, $J = 7.1$ Hz, 2H) ppm; MS (EI): $m/z = 214$ (M^+).

Ethyl 2-[4-(2-pyridyl)piperazino]acetate (**9**, $C_{13}H_{19}N_3O_2$)
Oil; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.23$ (t, $J = 7.55$ Hz, 3H), 2.88 (t, $J = 4.53$ Hz, 4H), 3.15 (s, 2H), 3.39 (t, $J = 4.53$ Hz, 4H), 4.12 (q, $J = 7.53$ Hz, 2H), 6.49 (m, 2H), 7.34 (t, $J = 9.03$ Hz, 1H), 8.07 (d, $J = 6.04$ Hz, 1H) ppm; MS (EI): $m/z = 249$ (M^+).

tert-Butyl 4-(2-ethoxy-2-oxoethyl)-1-piperazinecarboxylate (**10**, $C_{12}H_{18}N_4O_2$)
Oil; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.29$ (t, $J = 7.2$ Hz, 3H), 1.49 (s, 9H), 2.63–2.75 (m, 4H), 3.18 (s, 2H), 3.20–3.31 (m, 4H), 4.18 (q, $J = 7.3$ Hz, 2H) ppm; MS (EI): $m/z = 272$ (M^+).

Ethyl 2-[4-(2-pyrimidinyl)piperazino]acetate (**12**, $C_{12}H_{18}N_4O_2$)
Oil; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.29$ (t, $J = 7.55$ Hz, 3H), 2.63 (t, $J = 5.28$ Hz, 4H), 3.21 (s, 2H), 3.85 (t, $J = 5.28$ Hz, 4H), 4.17 (q, $J = 7.55$ Hz, 2H), 6.42 (t, $J = 5.28$ Hz, 1H), 8.24 (d, $J = 4.53$ Hz, 2H) ppm; MS (EI): $m/z = 250$ (M^+).

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