Rhodium-Catalyzed Synthesis of α-Amido- and α-Carboxylic-β-Ketoesters

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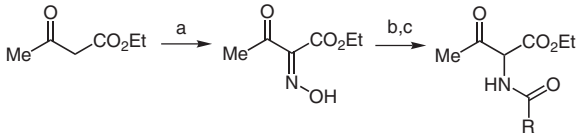
Abstract: The rhodium-catalyzed N–H and O–H insertion of amides and carboxylic acids with α-diazo-β-ketoesters to give different α-amido- and α-carboxylic-β-ketoesters is presented. Investigations were carried out to establish an efficient N–H and O–H insertion reaction using a range of different amides and carboxylic acids for the synthesis of intermediates e.g. for receptor antagonists. The reactions were performed under mild conditions with 1 mol% of catalyst and the products were formed in good yields.

Keywords: amides, carboxylic acids, catalysis, diazo compounds, insertions, rhodium

α-Amido-β-ketoesters are important starting materials or intermediates for the synthesis of a wide variety of compounds.[1] One example is the use of these compounds as precursors for high affinity NPY Y5 receptor antagonists that might play a role in the regulation of human metabolism.[2] They are also under investigation for the treatment of obesity. However, the use of the receptor antagonists for treatment of the latter has been subject to debate.[3] The conventional approach towards the synthesis of α-amido-β-ketoesters is presented in Equation 1.[4]

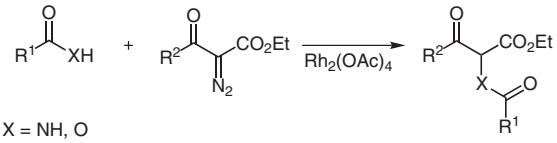


a: $NaNO_2$, AcOH, H_2O; b: Zn, H_2SO_4, H_2O; c: R(C = O)Cl

Equation 1

This route requires three steps and gives an overall yield of less than 50%. The necessity of an easy route giving α-amido-β-ketoesters in higher yields, as well as, allowing a broad range of R-substituents is therefore desirable. In this paper we present a Rh(II)-catalyzed X–H (X = N, O) insertion which generally gives high yields (Equation 2).

According to our knowledge, N–H insertions have mostly been used commercially by Merck chemists in intramolecular cyclization reactions for the total synthesis of thienamycin.[5] The increasing importance of intra- and intermolecular metal-carbenoid insertions into N–H bonds is illustrated by numerous new studies in this area.[6,7] In this paper we report a range of different substituted amides and carboxylic acids as substrates for N–H and O–H insertions with different β-keto-α-diazoesters, making it applicable to the synthesis of more complex molecules.

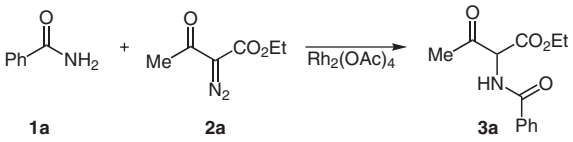


X = NH, O

Equation 2

A number of different metal catalysts were screened[8] and it was found that the only metal catalyst giving a reasonable yield of the desired product was Rh(II).

After choosing Rh(II) as the catalyst we focused on optimizing conditions for the reaction of benzamide (**1a**) with ethyl diazoacetoacetate (**2a**) (Equation 3).



1a **2a** **3a**

Equation 3

In the screening process for the N–H insertion, solvents, catalyst loading, reaction temperature and other parameters were tested. Table 1 shows some representative results.

It is well known that Rh(II)-carbenoid reactions perform usually best in halogenated solvents.[6] A solvent effect was observed and CH_2Cl_2 was found to be superior compared to toluene and dichloroethane (Table 1, entries 1, 5 and 6). Toluene afforded a range of minor impurities, many of them are supposed to be the products of insertion into the aromatic C–H bonds of the solvent.[10] Increasing the temperature from ambient temperature to 40 °C improved the yield of the reaction (entries 2 and 6). It was also observed that excess of **1a** had no effect on the yield of the reaction compared to stoichiometric amounts. Surprisingly, the use of 1 mol% of catalyst gave better yield than with 5 mol% (entries 3 and 6). Finally, it should be noted that the optimal administration of **2a** was by achieved via slow addition (entry 10).[11]

A number of different amides and carboxylic acids were reacted with ethyl diazoacetoacetate (**2a**) in the presence of 1 mol% $Rh_2(OAc)_4$ as the catalyst (Equation 4). Some

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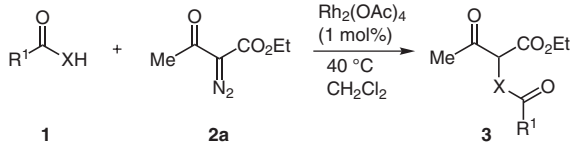
Table 1 Screening Results for N–H Insertion of Benzamide (**1a**) with Ethyl Diazoacetoacetate (**2a**) Catalyzed by $Rh_2(OAc)_4$

Entry	Cat. (mol%)	**1a/2a**	Temp (°C)	Time	Solvent	Yield[a] (%)
1	5	1	80	16 h	Toluene	–[b]
2	5	1	r.t.	3 d	CH_2Cl_2	55
3	5	1	40	16 h	CH_2Cl_2	60
4[c]	2	1	40	40 h	CH_2Cl_2	65
5	1	1	80	16 h	$Cl(CH_2)_2Cl$	60
6	1	1	40	16 h	CH_2Cl_2	72
7	1	1	40	3 d	CH_2Cl_2	68
8	1	15	40	16 h	CH_2Cl_2	64
9	1	1	40	3.5 h	CH_2Cl_2	63
10[d]	1	1	40	16 h	CH_2Cl_2	77
11[e]	1	1	40	16 h	CH_2Cl_2	66

[a] Isolated yield.
[b] Ca. 60% of partially purified product obtained.
[c] Catalyst (0.01 mmol) added twice with 24 h interval.
[d] Slow addition of **2a**.
[e] PhOH (25 mol%) added.[9]

substrates were selected from NPY Y5 receptor affinities of known antagonists.[2] Others were chosen in order to study substitution effects. Furthermore, we have tried to expand the scope to S–H insertions. The results are found in Table 2.



Equation 4

The screening showed that for the amides, aromatic substituents gave superior results compared with alkyl substituents (Table 2, entries 1, 6 and 7). Inspection of the different substituents on the aromatic part showed that electron-withdrawing groups tend to give higher yields than compounds substituted with electron-donating groups. Furthermore, *ortho*-substituted aromatic functionalities generally gave lower yields (entries 4 and 5). The moderate yield in entry 4 is either due to the electron-donation effect or to the steric hindrance by the bulky group in the *ortho* position (OEt).

Changing the reagent to benzoic acid and its derivatives improved the yield slightly (Table 2, entries 8–12), showing a positive effect probably due to the acidity of the proton.[6] The highest yield (90%) was obtained for 3,4-dichloro benzoic acid (entry 10). As seen in entry 11, a nitro group in the substrate gives lower yield despite its electron-withdrawing effect. This is thought to be due to a

Table 2 Screening of Different Substrates for the X–H Insertion with Ethyl Diazoacetoacetate (**2a**) Catalyzed by $Rh_2(OAc)_4$[a]

Entry	Substrate	X	R^1	Yield [b](%)
1	**1a**	NH	Ph	**3a** (72)
2	**1b**	NH	1-Naphthyl	**3b** (55)
3	**1c**	NH	3,4-diF-Ph	**3c** (70)
4	**1d**	NH	2-EtOPh	**3d** (36)
5	**1e**	NH	2-NO_2Ph	**3e** (46)
6	**1f**	NH	Me	**3f** (51)
7	**1g**	NH	CH_2Cl	**3g** (37)
8	**1h**	O	Ph	**3h** (75)
9	**1i**	O	1-Naphthyl	**3i** (74)
10	**1j**	O	3,4-diCl-Ph	**3j** (90)
11	**1k**	O	4-NO_2Ph	**3k** (62)
12	**1l**	O	4-MeOPh	**3l** (68)
13	**1m**	S	Ph	–

[a] See experimental section for reaction conditions.
[b] Isolated yield.

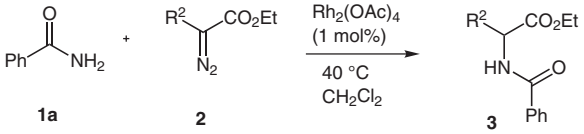
coordination of the nitro group with $Rh_2(OAc)_4$ leading to inactivation.

It was found that the benzoic acids did not react with the diazo compounds in the absence of Rh(II), even though reactions between carboxylic acids and diazo compounds have been reported.[12] It should also be noted that the use of only 0.1 mol% $Rh_2(OAc)_4$ as catalyst for the reaction of benzoic acid (**1h**) with ethyl diazoacetoacetate (**2a**) gave 54% yield of **3h**.

Thiobenzoic acid (**1m**) did not react under the present reaction conditions. This could be due to a coordination between sulfur and the Rh(II)-catalyst.

During our investigations we did not observe any effect upon adding phenol to the reaction mixture, even though such an effect has been described.[9] Therefore, we envisioned that using *para*-hydroxybenzamide as substrate in our reaction could give information about electronic effects of the aromatic substituents, as well as, the possibility of an aromatic O–H insertion (in competition with the N–H insertion). A moderate yield of 35% was obtained and investigations by ^{1}H NMR spectroscopy revealed the product to be a 2:1 mixture of N–H to O–H insertion product. The yield indicates a negative effect on the N–H insertion due to the electron-donating property of the hydroxyl group, whereas the presence of an O–H insertion product indicates a positive effect of the electron-withdrawing property of the amide substituent.[13]

To increase the scope of the reaction, different α-diazo-esters **2** were reacted with benzamide **1a** to test for substituent effects at the β-position (Equation 5). The results are found in Table 3.



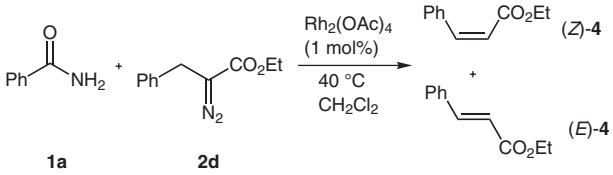
Equation 5

Table 3 Screening of Different α-Diazo Compounds for the N–H Insertion into Benzamide (**1a**)[a]

Entry	Substrate	R^2	Product	Yield[b] (%)
1	**2a**	Ac	**3a**	72
2	**2b**	$(CO)CH_2Cl$	**3n**	64
3	**2c**	H	**3o**	33[c]
4	**2d**	Bn	**3p**	–

[a] See experimental section for reaction conditions.
[b] Isolated yield.
[c] The product **3o** was isolated as a mixture of the *sec*- and *tert*-amide products (30% of the latter).

Based on the results in Table 3 we stress the importance of the carbonyl group at the β-position in the α-diazoester-compounds.[14] As reported recently by our group, diazo compound **2d** is prone to form an unwanted side-product[7a] (Equation 6).



Equation 6

The use of $Rh_2(OAc)_4$ as the catalyst gave 36% (*Z*)- and (*E*)-3-phenylacrylic acid ethyl esters **4** with a 2.3:1 selectivity for the *Z*-isomer (determined by ^{1}H NMR spectroscopy).[15]

Diazoacetate **2c** gave a mixture of single and double insertion products. The existence of the tertiary amide gave us hope that the reaction could be expanded to N–H insertion to secondary amides. However, we have found that *N*-methyl amides in general reacted considerably slower than the non-alkylated ones. Only traces of N-methylated products could be found among many impurities, even after prolonged reaction times.

In summary, we have established an easy general route to important building blocks for the synthesis of, for example, receptor antagonists. The formed α-amido-β-ketoesters were obtained in moderate to good yields. Aromatic amides gave generally higher yields than aliphatic ones. The substitution pattern of the diazo compound was found to be important as well, and best results were obtained with ethyl α-diazoacetoacetate. Furthermore, a general synthetic method towards the formation of α-carboxy-β-ketoesters via a catalytic Rh(II)-carbenoid O–H insertion has been developed.

Commercially available compounds were used without further purification. Solvents were dried according to standard procedures. Purification of the products was carried out by flash chromatography using Merck silica gel 60 (230–400 mesh). TLC was performed using Merck silica gel 60 F254 plates and visualized under UV light and with different stains. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Mercury at 400 MHz and 100 MHz, respectively, using $CDCl_3$ as the solvent, and are reported in ppm relative to the solvent peak of $CDCl_3$ (δ = 7.26 for ^{1}H NMR and δ = 77.0 for the central resonance in ^{13}C NMR). Mass spectral data was collected on a Micromass LCT.

X–H (X = N, O, S) Insertions; General Procedure

The carbonyl compound **1** (1 mmol) and $Rh_2(OAc)_4$ (0.01 mmol, 1 mol%) were stirred in anhyd CH_2Cl_2 (2 mL) in a flame dried Schlenk tube under a N_2 atmosphere. The solution was warmed to the desired temperature (40 °C) and the diazo compound **2** (1 mmol) was added. The reaction mixture was stirred overnight. Purification was done by flash chromatography.

The purification of 3,4-dichloro-benzoic acid 1-ethoxycarbonyl-2-oxo-propyl ester (**3j**) was done by filtering and washing with CH_2Cl_2. 2-Benzoylamino-4-chloro-3-oxo-butyric acid ethyl ester

(**3n**) was found to be unstable in normal silica and was therefore purified using iatrobeads.

2-Benzoylamino-3-oxobutyric Acid Ethyl Ester (3a)
^{1}H NMR: δ = 7.79 (d, *J* = 7.3 Hz, 2 H, ArH), 7.32–7.48 (m, 4 H, ArH, NH), 5.39 (d, *J* = 6.4 Hz, 1 H, CH), 4,22 (dq, *J* = 7.2, 3.0 Hz, 2 H, CH_2), 2.38 (s, 3 H, $COCH_3$), 1.24 (t, *J* = 7.1 Hz, 3 H, CH_3).

^{13}C NMR: δ = 198.5, 166.6, 165.9, 132.7, 131.8, 128.4 (2 × C), 127.1 (2 × C), 63.3, 62.4, 27.8, 13.7.

HRMS: *m*/*z* calcd for $C_{13}H_{15}NNaO_4$: 272.0899; found: 272.0891.

2-[(Naphthalene-1-carbonyl)amino]-3-oxobutyric Acid Ethyl Ester (3b)
^{1}H NMR: δ = 8.37 (d, *J* = 8.1 Hz, 1 H, ArH), 7.93 (d, *J* = 8.3 Hz, 1 H, ArH), 7.86 (d, *J* = 7.3 Hz, 1 H, ArH), 7.71 (d, *J* = 7.0 Hz, 1 H, ArH), 7.50–7.60 (m, 2 H, ArH), 7.41–7.48 (m, 1 H, ArH), 7.23 (d, *J* = 6.3 Hz, 1 H, NH), 5.54 (d, *J* = 6.5 Hz, 1 H, CH), 4.32 (dq, *J* = 7.1, 5.4 Hz, 2 H, CH_2), 2.48 (s, 3 H, $COCH_3$), 1.34 (t, *J* = 7.2 Hz, 3 H, CH_3).

^{13}C NMR: δ = 198.7, 169.3, 166.2, 133.9, 133.0, 131.5, 130.4, 128.6, 127.6, 126.7, 125.9, 125.5, 124.9, 64.0, 63.1, 28.5, 14.3.

HRMS: *m*/*z* calcd for $C_{17}H_{17}NNaO_4$: 322.1055; found: 322.1046.

2-(3,4-Difluorobenzoylamino)-3-oxobutyric Acid Ethyl Ester (3c)
^{1}H NMR: δ = 7.66 (ddd, *J* = 10.6, 7.5, 2.2 Hz, 1 H, ArH), 7.54–7.59 (m, 1 H, ArH), 7.42 (d, *J* = 6.4 Hz, 1 H, NH), 7.13–7.22 (m, 1 H, ArH), 5.38 (d, *J* = 6.5 Hz, 1 H, CH), 4.23 (dq, *J* = 7.2, 2.6 Hz, 2 H, CH_2), 2.39 (s, 3 H, $COCH_3$), 1.26 (t, *J* = 7.1 Hz, 3 H, CH_3).

^{13}C NMR: δ = 198.3, 165.8, 164.6, 152,6 (dd, $^1J_{CF}$ = 254.9 Hz, $^2J_{CF}$ = 12.9 Hz), 150.0 (dd, $^1J_{CF}$ = 250.3 Hz, $^2J_{CF}$ = 13.1 Hz), 129.8 (dd, $^3J_{CF}$ = 5.0 Hz, $^4J_{CF}$ = 3.5 Hz), 123.8 (dd, $^3J_{CF}$ = 7.3 Hz, $^4J_{CF}$ = 3.7 Hz), 117.3 (d, $^2J_{CF}$ = 17.8 Hz), 117.0 (d, $^2J_{CF}$ = 18.9 Hz), 63.4, 62.7, 27.9, 13.8.

HRMS: *m*/*z* calcd for $C_{13}H_{13}F_2NNaO_4$: 308.0710; found: 308.0726.

2-(2-Ethoxybenzoylamino)-3-oxobutyric Acid Ethyl Ester (3d)
^{1}H NMR: δ = 9.30 (d, *J* = 5.4 Hz, 1 H, NH), 8.15 (dd, *J* = 7.9, 1.9 Hz, 1 H, ArH), 7.42 (ddd, *J* = 8.6, 7.5, 1.9 Hz, 1 H, ArH), 7.02 (dt, *J* = 7.5, 0.9 Hz, 1 H, ArH), 6.96 (d, *J* = 8.3 Hz, 1 H, ArH), 5.41 (d, *J* = 5.7 Hz, 1 H, CH), 4.28 (q, *J* = 7.1 Hz, 2 H, CH_2), 4.20 (q, *J* = 7.0 Hz, 2 H, CH_2), 2.42 (s, 3 H, $COCH_3$), 1.61 (t, *J* = 7.0 Hz, 3 H, CH_3), 1.30 (t, *J* = 7.1 Hz, 3 H, CH_3).

^{13}C NMR: δ = 198.8, 166.2, 164.8, 157.5, 133.3, 132.1, 120.8, 119.9, 112.1, 64.8, 64.1, 62.4, 28.0, 14.6, 14.0.

HRMS: *m*/*z* calcd for $C_{15}H_{19}NNaO_5$: 316.1161; found: 316.1160.

2-(2-Nitrobenzoylamino)-3-oxobutyric Acid Ethyl Ester (3e)
^{1}H NMR: δ = 8.02 (d, *J* = 8.3 Hz, 1 H, ArH), 7.67 (dt, *J* = 7.5, 1.7 Hz, 1 H, ArH), 7.58 (dt, *J* = 7.5, 1.5 Hz, 2 H, ArH), 7.14 (d, *J* = 6.2 Hz, 1 H, NH), 5.42 (d, *J* = 6.5 Hz, 1 H, CH), 4.28 (dq, *J* = 7.1, 1.9 Hz, 2 H, CH_2), 2.43 (s, 3 H, $COCH_3$), 1.31 (t, *J* = 7.1 Hz, 3 H, CH_3).

^{13}C NMR: δ = 198.0, 165.8, 165.5, 146.3, 133.6, 131.5, 130.9, 128.8, 124.5, 63.3, 62.8, 28.0, 13.9.

HRMS: *m*/*z* calcd for $C_{13}H_{14}N_2NaO_6$: 317.0750; found: 317.0747.

2-Acetylamino-3-oxobutyric Acid Ethyl Ester (3f)
^{1}H NMR: δ = 6.90 (d, *J* = 5.6 Hz, 1 H, NH), 5.19 (d, *J* = 6.7 Hz, 1 H, CH), 4.18 (dq, *J* = 7.1, 1.1 Hz, 2 H, CH_2), 2.30 (s, 3 H, $COCH_3$), 1.99 (s, 3 H, $COCH_3$), 1.23 (t, *J* = 7.1 Hz, 3 H, CH_3).

^{13}C NMR: δ = 198.7, 169.9, 166.0, 63.0, 62.5, 28.0, 22.5, 13.8.

HRMS: *m*/*z* calcd for $C_8H_{13}NNaO_4$: 210.0742; found: 210.0732.

2-(2-Chloroacetylamino)-3-oxobutyric Acid Ethyl Ester (3g)
^{1}H NMR: δ = 7.66 (d, *J* = 3.6 Hz, 1 H, NH), 5.19 (d, *J* = 6.4 Hz, 1 H, CH), 4.26 (dq, *J* = 7.0, 1.5 Hz, 2 H, CH_2), 4.07 (s, 2 H, CH_2Cl), 2.38 (s, 3 H, $COCH_3$), 1.29 (t, *J* = 7.1 Hz, 3 H, CH_3).

^{13}C NMR: δ = 197.4, 165.9, 165.2, 63.1, 62.8, 42.0, 27.9, 13.9.

HRMS: *m*/*z* calcd for $C_8H_{12}ClNNaO_4$: 244.0353; found: 244.0348.

Benzoic Acid 1-Ethoxycarbonyl-2-oxopropyl Ester (3h)
^{1}H NMR: δ = 8.10 (dd, *J* = 8.4, 1.3 Hz, 2 H, ArH), 7.55–7.62 (m, 1 H, ArH), 7.45 (t, *J* = 7.7 Hz, 2 H, ArH), 5.69 (s, 1 H, CH), 4.28 (q, *J* = 7.1 Hz, 2 H, CH_2), 2.40 (s, 3 H, $COCH_3$), 1.29 (t, *J* = 7.1 Hz, 3 H, CH_3).

^{13}C NMR: δ = 197.6, 164.9, 164.4, 133.7, 129.9, 128.4, 128.3, 78.0, 62.4, 27.2, 13.9.

HRMS: *m*/*z* calcd for $C_{13}H_{14}NaO_5$: 273.0739; found: 273.0745.

Naphthalene-1-carboxylic Acid 1-Ethoxycarbonyl-2-oxopropyl Ester (3i)
^{1}H NMR: δ = 8.94 (d, *J* = 8.7 Hz, 1 H, ArH), 8.40 (dd, *J* = 7.3, 1.2 Hz, 1 H, ArH), 8.06 (d, *J* = 8.2 Hz, 1 H, ArH), 7.89 (d, *J* = 8.1 Hz, 1 H, ArH), 7.63 (ddd, *J* = 8.5, 6.9, 1.2 Hz, 1 H, ArH), 7.49–7.58 (m, 2 H, ArH), 5.84 (s, 1 H, CH), 4.34 (q, *J* = 7.1 Hz, 2 H, CH_2), 2.46 (s, 3 H, $COCH_3$), 1.34 (t, *J* = 7.1 Hz, 3 H, CH_3).

^{13}C NMR: δ = 197.7, 165.7, 164.6, 134.4, 133.7, 131.3, 131.2, 128.6, 128.1, 126.3, 125.4, 124.9, 124.4, 78.2, 62.5, 27.4, 13.9.

HRMS: *m*/*z* calcd for $C_{17}H_{16}NaO_5$: 323.0895; found: 323.0894.

3,4-Dichlorobenzoic Acid 1-Ethoxycarbonyl-2-oxopropyl Ester (3j)
^{1}H NMR: δ = 8.16 (s, 1 H, ArH), 7.92 (d, *J* = 8.3 Hz, 1 H, ArH), 7.54 (d, *J* = 8.4 Hz, 1 H, ArH), 5.71 (s, 1 H, CH), 4.30 (q, *J* = 7.1 Hz, 2 H, CH_2), 2.41 (s, 3 H, $COCH_3$), 1.30 (t, *J* = 7.1 Hz, 3 H, CH_3).

^{13}C NMR: δ = 196.8, 164.0, 163.2, 138.5, 133.1, 131.8, 130.7, 129.0, 128.2, 78.3, 62.7, 27.3, 13.9.

HRMS: *m*/*z* calcd for $C_{13}H_{12}Cl_2NaO_5$: 340.9959; found: 340.9967.

4-Nitrobenzoic Acid 1-Ethoxycarbonyl-2-oxopropyl Ester (3k)
^{1}H NMR: δ = 8.26–8.31 (m, 4 H, ArH), 5.76 (s, 1 H, CH), 4.31 (q, *J* = 7.1 Hz, 2 H, CH_2), 2.43 (s, 3 H, $COCH_3$), 1.33 (t, *J* = 7.1 Hz, 3 H, CH_3).

^{13}C NMR: δ = 196.4, 163.8, 163.2, 150.9, 133.7, 131.1 (2 × C), 123.6 (2 × C), 78.5, 62.8, 27.4, 13.9.

HRMS: *m*/*z* calcd for $C_{13}H_{13}NNaO_7$: 318.0590; found: 318.0599.

4-Methoxybenzoic Acid 1-Ethoxycarbonyl-2-oxopropyl Ester (3l)
^{1}H NMR: δ = 8.04 (d, *J* = 8.8 Hz, 2 H, ArH), 6.91 (d, *J* = 8.8 Hz, 2 H, ArH), 5.65 (s, 1 H, CH), 4.27 (q, *J* = 7.1 Hz, 2 H, CH_2), 3.83 (s, 3 H, OCH_3), 2.39 (s, 3 H, $COCH_3$), 1.28 (t, *J* = 7.1 Hz, 3 H, CH_3).

^{13}C NMR: δ = 198.0, 164.6 (2 × C), 163.9, 132.1 (2 × C), 120.5, 113.7 (2 × C), 77.9, 62.3, 55.3, 27.2, 13.9.

HRMS: *m*/*z* calcd for $C_{14}H_{16}NaO_6$: 303.0845; found: 303.0847.

2-Benzoylamino-4-chloro-3-oxobutyric Acid Ethyl Ester (3n)
^{1}H NMR: δ = 7.79–7.83 (m, 2 H, ArH), 7.50–7.54 (m, 1 H, ArH), 7.41–7.46 (m, 2 H, ArH), 7.38 (d, *J* = 5.7 Hz, 1 H, NH), 5.59 (d, *J* = 6.4 Hz, 1 H, CH), 4.57 (s, 2 H, CH_2Cl), 4.28 (q, *J* = 7.1 Hz, 2 H, CH_2), 1.29 (t, *J* = 7.1 Hz, 3 H, CH_3).

^{13}C NMR: δ = 193.9, 167.0, 165.3, 132.7, 132.3, 128.6 (2 × C), 127.2 (2 × C), 63.2, 60.2, 47.5, 13.9.

HRMS: *m*/*z* calcd for $C_{13}H_{14}ClNNaO_4$: 306.0509; found: 306.0504.

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