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Tetrahedron 64 (2008) 1765–1771
Tetrahedron
www.elsevier.com/locate/tet

Electroreductive acylation of aromatic imines with acylimidazoles

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Received 15 November 2007; received in revised form 29 November 2007; accepted 29 November 2007
Available online 5 December 2007

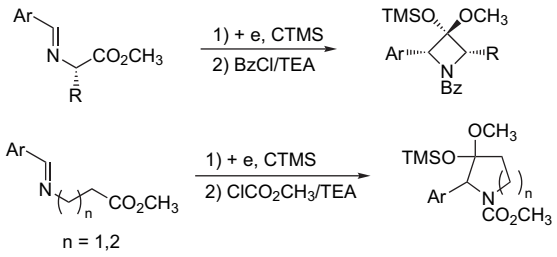
Dedicated to the memory of Professor Yoshihiro Matsumura

Abstract

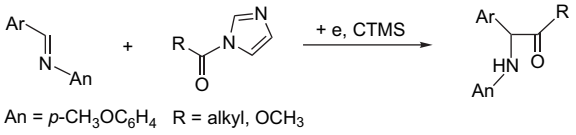
The intermolecular reductive coupling of aromatic imines with acylimidazoles was effected by electroreduction in the presence of chlorotrimethylsilane and gave α-amino-α-aryl ketones. This method was also effective for the synthesis of α-amino-α-aryl esters using methoxycarbonylimidazole as an electrophile.

1. Introduction

Recently, we have reported that the electroreduction in the presence of chlorotrimethylsilane (CTMS) is a useful method for the reductive intramolecular coupling of aromatic α-, β-, and γ-imino esters (Scheme 1).[1] However, this reaction was limited to intramolecular coupling to give four-, five-, and six-membered cyclic amines. We therefore attempted intermolecular coupling of aromatic imines with carboxylic acid derivatives more reactive than esters, since this type of reaction has so far been unknown except for our electrochemical method. We wish to report in this paper that the electroreduction of aromatic imines with acylimidazoles in the presence of CTMS effected intermolecular reductive C-acylation of aromatic imines (Scheme 2).[2,3] This electroreduction provides a useful method for the synthesis of α-amino-α-aryl ketones[4,5] and esters.



Scheme 1. Electroreductive intramolecular coupling of α-, β-, and γ-iminoesters.



Scheme 2. Electroreductive intermolecular coupling of aromatic imines with *N*-acylimidazoles.

2. Results and discussion

Initially, the electroreductive C-acylation of *N*-benzylidene-4-methoxybenzenamine (**1a**) was surveyed with several *N*-acylimidazoles and acid anhydrides in the presence of CTMS and triethylamine (TEA). The results are summarized in Table 1. The electroreduction was carried out according to the reported conditions for the electroreductive intramolecular coupling of aromatic iminoesters:[1] using Pb cathode and a divided cell in THF containing Bu_4NPF_6 as a supporting electrolyte. *C*-Acetylated product **2a** was obtained in 60% yield by the reaction with acetylimidazole (run 1). In the absence of CTMS, **2a** was not obtained and simply reduced amine, *N*-benzyl-4-methoxybenzenamine, was formed predominantly in 90% yield (run 2). On the other hand, the absence of TEA brought about slightly decrease of the yield of

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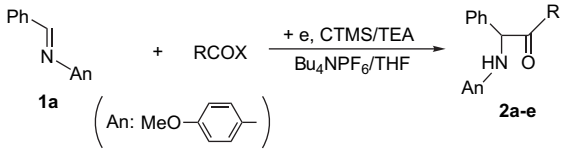
doi:10.1016/j.tet.2007.11.106

Table 1
Electroreduction of **1a** with *N*-acylimidazoles and acid anhydrides



Run	RCOX[a]	Yield[b] (%) of **2**
1	CH_3COIm	**2a** (60)
2[c]	CH_3COIm	**2a** (0) (90)[d]
3[e]	CH_3COIm	**2a** (53)
4[f]	CH_3COIm	**2a** (58)
5[g]	CH_3COIm	**2a** (55)
6	$(CH_3CO)_2O$	**2a** (25) (60)[d]
7	C_2H_5COIm	**2b** (73)
8	$(C_2H_5CO)_2O$	**2b** (58)
9	n-C_3H_7COIm	**2c** (82)
10	$(n$-$C_3H_7CO)_2O$	**2c** (60)
11	i-C_3H_7COIm	**2d** (76)
12	$(i$-$C_3H_7CO)_2O$	**2d** (55)
13	n-$C_7H_{15}COIm$	**2e** (66)
14	$(n$-$C_7H_{15}CO)_2O$	**2e** (52)

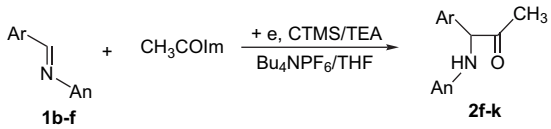
[a] Five equivalents.
[b] Isolated yields.
[c] In the absence of CTMS.
[d] Yield of simply reduced amine.
[e] In the absence of TEA.
[f] Using Bu_4NClO_4 in place of Bu_4NPF_6.
[g] Using Et_4NOTs/DMF in place of Bu_4NPF_6/THF.

2a (run 3). These results show that in the intermolecular electroreductive coupling of **1a** also the presence of CTMS was essential, while the presence of triethylamine was not necessarily essential. The use of Bu_4NClO_4 as a supporting electrolyte in place of Bu_4NPF_6 provided the result comparable to run 1 (run 4). When the electroreduction was carried out in DMF containing Et_4NOTs according to the preliminary report,[3] the yield of **2a** was somewhat less than that in run 1 (run 5). Although the same product **2a** was obtained by the reaction of **1a** with acetic anhydride (run 6), the yield of **2a** (25%) was much lower than in run 1 and simply reduced amine was obtained as a major product (60% yield). As shown in Table 1, acylimidazoles are generally better acylating agents than acid anhydrides and gave the corresponding *C*-acylated products **2** in moderate-to-good yields.

Next, several *N*-arylmethylidene-4-methoxybenzenamines **1b–f** were subjected to the reductive C-acetylation with acetylimidazole (Table 2). *para* and *ortho* Substitutions of methoxy group and *para* substitution of cyano group decreased the yields of α-amino-α-aryl ketones **2f**, **2g**, and **2k** (runs 1, 2, and 6), whereas 3,4-dimethoxy and *para*-fluoro substitutions did not inhibit the reductive acylation (runs 3 and 4). 1-Naphthyl imine **1f** gave the corresponding α-amino ketone **2j** in 72% yield (run 5).

Esters are completely inert under the present conditions. In fact, the electroreduction of **1a** with methyl acetate in the presence of CTMS–TEA afforded no *C*-acetylated product **2a**. In accord with the results, the electroreduction of **1a–f** with acylimidazoles derived from succinic acid and glutaric acid monomethyl esters was attempted (Table 3). Expectedly, α-amino-α-aryl ketones **2l–r** possessing an ester group were obtained chemoselectively.

Table 2
Electroreduction of aromatic imines with acetylimidazoles



Run	**1**	Ar	Yield[a] (%) of **2**
1	**1b**	p-$MeOC_6H_4$	**2f** (50)
2	**1c**	o-$MeOC_6H_4$	**2g** (37)
3	**1d**	3,4-$(MeO)_2C_6H_3$	**2h** (60)
4	**1e**	p-FC_6H_4	**2i** (64)
5	**1f**	1-Naphthyl	**2j** (72)
6	**1g**	p-NCC_6H_4	**2k** (44)

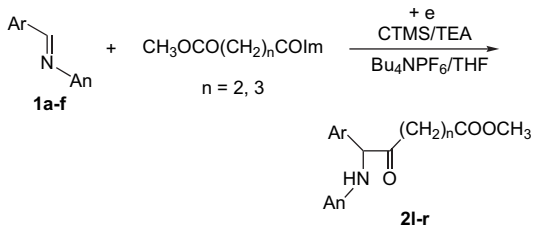
[a] Isolated yields.

The electroreduction of **1a–f**,**h** with methoxycarbonylimidazole gave the corresponding *C*-methoxycarbonylated products **3**. The results are exhibited in Table 4. By this method, α-amino-α-aryl methyl esters **3a–f**,**h** were obtained in moderate-to-good yields. Recently, Nishiguchi and coworkers have reported that the electroreduction of aromatic imines with methoxycarbonylimidazole using an undivided cell equipped with Zn electrodes gave geminal *C*-dimethoxycarbonylated products, aryl aminomalonic dimethyl esters.[6] On the contrary, the *C*-monomethoxycarbonylated products **3**, *N*-(*p*-methoxyphenyl)-2-arylglycine methyl esters, were obtained by our method.

Removal of *N*-*p*-methoxyphenyl (An) group in the acylated products **2** and **3** was readily achieved by oxidation with CAN after formylation. Several examples are shown in Scheme 3. Therefore, this method provides a new synthetic route to α-amino-α-aryl ketones and 2-arylglycine methyl esters.

The reaction mechanism of the electroreductive intermolecular coupling can be speculated in Scheme 4, similar to the previously reported intramolecular coupling of iminoesters.[1]

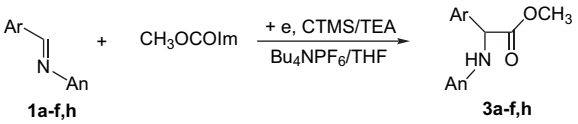
Table 3
Electroreduction of aromatic imines with acylimidazoles possesing a methoxycarbonyl group



Run	**1**	Ar	n	Yield[a] (%) of **2**
1	**1a**	Ph	2	**2l** (55)
2	**1b**	p-$MeOC_6H_4$	2	**2m** (42)
3	**1c**	o-$MeOC_6H_4$	2	**2n** (62)
4	**1d**	3,4-$(MeO)_2C_6H_3$	2	**2o** (47)
5	**1e**	p-FC_6H_4	2	**2p** (50)
6	**1f**	1-Naphthyl	2	**2q** (73)
7	**1a**	Ph	3	**2r** (47)

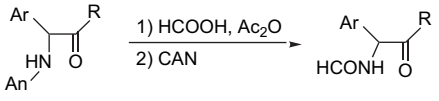
[a] Isolated yields.

Table 4
Electroreduction of aromatic imines with methoxycarbonylimidazole



Run	1	Ar	Yield[a] (%) of 3
1	**1a**	Ph	**3a** (62)
2	**1b**	*p*-$MeOC_6H_4$	**3b** (55)
3	**1c**	*o*-$MeOC_6H_4$	**3c** (56)
4	**1d**	3,4-$(MeO)_2C_6H_3$	**3d** (60)
5	**1e**	*p*-FC_6H_4	**3e** (65)
6	**1f**	1-Naphthyl	**3f** (50)
7	**1h**	2-Furyl	**3h** (40)

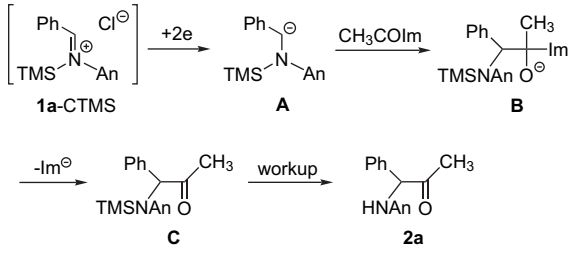
[a] Isolated yields.



2a Ar = Ph, R = CH_3 **4a** 54
2d Ar = Ph, R = *i*-C_3H_7 **4d** 60
3a Ar = Ph, R = OCH_3 **5a** 70
3e Ar = *p*-FC_6H_4, R = OCH_3 **5e** 68

Scheme 3. Formylation and oxidation with CAN of acylated products **2** and **3**.

Two-electron transfer to imine (**1a**)–CTMS complex generates the anion **A**. Nucleophilic attack of the anion **A** to the carbonyl group of acetylimidazole forms *O*-anion **B**, which immediately turns to **C** by elimination of imidazole anion. The product **2a** is obtained by N-desilylation of **C** during workup.



Scheme 4. Reaction mechanism.

3. Conclusion

The electroreduction of aromatic imines with acylimidazoles in the presence of CTMS and TEA produces reductively *C*-acylated products of imines. The presence of CTMS in the catholyte is essential to promote the electroreductive coupling. α-Amino-α-aryl ketones and 2-arylglycine methyl esters were synthesized conveniently by this method.

4. Experimental section

4.1. General

Column chromatography was performed on silica gel 60. THF was freshly distilled from sodium benzophenone ketyl. CTMS and TEA were distilled from CaH_2.

4.2. Starting materials

Aromatic imines were synthesized from the corresponding aromatic aldehydes and *p*-anisidine by refluxing in benzene and purified by recrystallization from ethanol. Acetylimidazole is commercially available. The other acylimidazoles were prepared from the corresponding acid chlorides and imidazole (2 equiv) by stirring in THF.

4.3. Typical procedure for electroreduction (Table 1, run 1)

A 0.3 M solution of Bu_4NPF_6 in THF (15 mL) was placed in the cathodic chamber of a divided cell (40-mL beaker, 3-cm diameter, 6-cm height) equipped with a lead cathode (5×5 cm^2), a platinum anode (2×1 cm^2), and a ceramic cylindrical diaphragm (1.5-cm diameter). A 0.3 M solution of Bu_4NPF_6 in DMF (4 mL) was placed in the anodic chamber (inside the diaphragm). *N*-Benzylidene-4-methoxybenzenamine (**1a**) (211 mg, 1 mmol), acetylimidazole (550 mg, 5 mmol), CTMS (0.64 mL, 5 mmol), and triethylamine (0.70 mL, 5 mmol) were added to the cathodic chamber. After 300 C of electricity was passed at a constant current of 100 mA at room temperature, the catholyte was evaporated in vacuo. The residue was diluted with Et_2O (30 mL) and insoluble Bu_4NPF_6 was filtered off. The filtrate was evaporated in vacuo. The crude mixture was purified by column chromatography on silica gel (hexanes/ethyl acetate=5/1) to give **2a** in 60% yield. The acylated products were identified by spectroscopic and elemental analyses as follows.

4.3.1. 1-(4-Methoxyphenylamino)-1-phenylpropan-2-one (2a)

White solid. Mp 126–127 °C. R_f 0.35 (hexanes/ethyl acetate=2/1). IR (KBr) 3381, 1711, 1514, 816, 766, 706 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.12 (s, 3H), 3.69 (s, 3H), 4.94 (s, 1H), 5.15 (br s, 1H), 6.48–6.52 (m, 2H), 6.67–6.71 (m, 2H), 7.29–7.34 (m, 1H), 7.35–7.40 (m, 2H), 7.43–7.47 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 26.7 (q), 55.6 (q), 69.0 (d), 114.4 (d), 114.8 (d), 127.8 (d), 128.3 (d), 129.2 (d), 138.3 (s), 140.3 (s), 152.1 (s), 204.3 (s). Anal. Calcd for $C_{16}H_{17}NO_2$: C, 75.27%; H, 6.71%; N, 5.49%. Found: C, 75.35%; H, 6.68%; N, 5.51%.

4.3.2. 1-(4-Methoxyphenylamino)-1-phenylbutan-2-one (2b)

Pale yellow paste. R_f 0.4 (hexanes/ethyl acetate=5/1). IR (neat) 3377, 1717, 1618, 1514, 818, 770, 758, 706 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.98 (t, 3H, *J*=7.3 Hz), 2.37–2.51 (m, 2H), 3.68 (s, 3H), 4.94 (s, 1H), 5.17 (br s, 1H), 6.48–6.52 (m, 2H), 6.66–6.70 (m, 2H), 7.27–7.31 (m, 1H), 7.34–7.38 (m, 2H), 7.42–7.45 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 7.6 (q), 32.2 (t), 55.3 (q), 68.0 (d), 114.3 (d), 114.5 (d), 127.6 (d), 128.0 (d), 128.9 (d), 138.4 (s), 140.2 (s), 151.9 (s), 207.0 (s). Anal. Calcd for $C_{17}H_{19}NO_2$: C, 75.81%; H, 7.11%; N, 5.20%. Found: C, 75.95%; H, 7.04%; N, 5.30%.

4.3.3. 1-(4-Methoxyphenylamino)-1-phenylpentan-2-one (2c)

Pale yellow paste. R_f 0.5 (hexanes/ethyl acetate=5/1). IR (neat) 3377, 1717, 1618, 1514, 818, 758, 704 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.77 (t, 3H, *J*=7.3 Hz), 1.42–1.62 (m, 2H),

2.32–2.46 (m, 2H), 3.68 (s, 3H), 4.93 (s, 1H), 5.29 (br s, 1H), 6.48–6.53 (m, 2H), 6.66–6.71 (m, 2H), 7.27–7.32 (m, 1H), 7.33–7.38 (m, 2H), 7.41–7.45 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 13.2 (q), 17.0 (t), 40.8 (t), 55.3 (q), 68.3 (d), 114.4 (d), 114.6 (d), 127.7 (d), 128.0 (d), 128.8 (d), 138.1 (s), 140.1 (s), 151.9 (s), 206.5 (s). Anal. Calcd for $C_{18}H_{21}NO_2$: C, 76.29%; H, 7.47%; N, 4.94%. Found: C, 76.44%; H, 7.35%; N, 4.84%.

*4.3.4. 1-(4-Methoxyphenylamino)-4-methyl-1-phenylpentan-2-one (**2d**)*

Pale yellow paste. R_f 0.35 (hexanes/ethyl acetate=5/1). IR (neat) 3395, 1715, 1514, 820, 766, 737, 718, 700 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 0.79 (d, 3H, J=6.9 Hz), 1.14 (d, 3H, J=6.9 Hz), 2.77–2.86 (m, 1H), 3.68 (s, 3H), 5.07 (s, 1H), 5.19 (br s, 1H), 6.50–6.54 (m, 2H), 6.67–6.71 (m, 2H), 7.26–7.31 (m, 1H), 7.33–7.37 (m, 2H), 7.41–7.44 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 18.2 (q), 19.3 (q), 36.9 (q), 55.5 (q), 66.9 (d), 114.4 (d), 114.7 (d), 127.9 (d), 128.1 (d), 128.9 (d), 138.0 (s), 140.2 (s), 152.0 (s), 210.3 (s). Anal. Calcd for $C_{18}H_{21}NO_2$: C, 76.29%; H, 7.47%; N, 4.94%. Found: C, 76.40%; H, 7.51%; N, 4.86%.

*4.3.5. 1-(4-Methoxyphenylamino)-1-phenylnonan-2-one (**2e**)*

Pale yellow paste. R_f 0.3 (hexanes/ethyl acetate=10/1). IR (neat) 3385, 1701, 1516, 826, 700 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 0.84 (t, 3H, J=7.3 Hz), 1.06–1.27 (m, 8H), 1.39–1.56 (m, 2H), 2.34–2.47 (m, 2H), 3.66 (s, 3H), 4.93 (s, 1H), 5.19 (br s, 1H), 6.48–6.52 (m, 2H), 6.66–6.70 (m, 2H), 7.27–7.31 (m, 1H), 7.33–7.38 (m, 2H), 7.41–7.44 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 13.9 (q), 22.4 (t), 23.7 (t), 28.8 (t), 31.5 (t), 39.0 (t), 55.6 (q), 68.4 (d), 114.4 (d), 114.7 (d), 127.8 (d), 128.1 (d), 129.0 (d), 138.3 (s), 140.3 (s), 152.0 (s), 206.7 (s). Anal. Calcd for $C_{22}H_{29}NO_2$: C, 77.84%; H, 8.61%; N, 4.13%. Found: C, 78.03%; H, 8.70%; N, 4.01%.

*4.3.6. 1-(4-Methoxyphenyl)-1-(4-methoxyphenylamino)-propan-2-one (**2f**)*

Pale yellow paste. R_f 0.2 (hexanes/ethyl acetate=5/1). IR (neat) 3373, 1713, 1676, 1601, 1512, 824, 737 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 2.11 (s, 3H), 3.69 (s, 3H), 3.80 (s, 3H), 4.89 (s, 1H), 5.08 (br s, 1H), 6.47–6.52 (m, 2H), 6.67–6.71 (m, 2H), 6.88–6.92 (m, 2H), 7.32–7.37 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 26.4 (q), 55.1 (q), 55.5 (q), 68.0 (d), 114.3 (d), 114.4 (d), 114.6 (d), 128.8 (d), 129.9 (s), 140.2 (s), 151.9 (s), 159.4 (s). Anal. Calcd for $C_{17}H_{19}NO_3$: C, 71.56%; H, 6.71%; N, 4.91%. Found: C, 71.68%; H, 6.62%; N, 4.97%.

*4.3.7. 1-(2-Methoxyphenyl)-1-(4-methoxyphenylamino)-propan-2-one (**2g**)*

White solid. Mp 109–110 °C. R_f 0.3 (hexanes/ethyl acetate=5/1). IR (KBr) 3402, 1711, 1597, 1516, 1489, 824, 806, 754 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 2.10 (s, 3H), 3.68 (s, 3H), 3.99 (s, 3H), 5.10 (br s, 1H), 5.50 (s, 1H), 6.46–6.51 (m, 2H), 6.65–6.70 (m, 2H), 6.89–6.93 (m, 1H), 6.94–6.98 (m, 1H), 7.23–7.29 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 26.4 (q), 55.5 (q), 61.4 (d), 110.7 (d), 114.2 (d), 114.7 (d), 121.3 (d), 126.2 (s), 128.0 (d), 129.2 (d), 140.4 (s), 151.9 (s), 156.9 (s), 204.5 (s). Anal. Calcd for $C_{17}H_{19}NO_3$: C, 71.56%; H, 6.71%; N, 4.91%. Found: C, 71.55%; H, 6.68%; N, 4.87%.

*4.3.8. 1-(3,4-Dimethoxyphenyl)-1-(4-methoxyphenylamino)-propan-2-one (**2h**)*

Pale yellow paste. R_f 0.3 (hexanes/ethyl acetate=2/1). IR (neat) 3369, 1719, 1593, 1512, 822, 766, 735, 702 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 2.12 (s, 3H), 3.69 (s, 3H), 3.85 (s, 3H), 3.87 (s, 3H), 4.86 (s, 1H), 6.49–6.54 (m, 2H), 6.67–6.72 (m, 2H), 6.85–6.89 (m, 2H), 7.03–7.06 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 26.2 (q), 55.2 (q), 55.5 (q), 68.2 (d), 109.7 (d), 111.1 (d), 114.2 (d), 114.4 (d), 120.2 (d), 130.3 (s), 140.1 (s), 148.7 (s), 149.3 (s), 151.8 (s), 204.4 (s). Anal. Calcd for $C_{18}H_{21}NO_4$: C, 68.55%; H, 6.71%; N, 4.44%. Found: C, 68.65%; H, 6.77%; N, 4.40%.

*4.3.9. 1-(4-Fluorophenyl)-1-(4-methoxyphenylamino)-propan-2-one (**2i**)*

Pale yellow paste. R_f 0.25 (hexanes/ethyl acetate=5/1). ^{1}H NMR ($CDCl_3$) δ 2.12 (s, 3H), 3.69 (s, 3H), 4.92 (s, 1H), 6.46–6.50 (m, 2H), 6.67–6.71 (m, 2H), 7.04–7.10 (m, 2H), 7.40–7.45 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 26.4 (q), 55.4 (q), 67.9 (d), 114.3 (d), 114.6 (d), 115.9 (d, J_{CCF}=21.0 Hz), 129.2 (d, J_{CCCF}=7.6 Hz), 133.9 (s, J_{CCCCF}=2.9 Hz), 133.9 (s), 152.1 (s), 162.4 (s, J_{CF}=245.1 Hz), 203.9 (s). Anal. Calcd for $C_{16}H_{16}NO_2$: C, 70.31%; H, 5.90%; N, 5.12%. Found: C, 70.36%; H, 5.85%; N, 5.10%.

*4.3.10. 1-(4-Methoxyphenylamino)-1-(naphthalen-1-yl)-propan-2-one (**2j**)*

Pale yellow paste. R_f 0.35 (hexanes/ethyl acetate=5/1). IR (neat) 3265, 1711, 1663, 1607, 1510, 831, 800, 781, 737 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 2.05 (s, 3H), 3.66 (s, 3H), 5.24 (br s, 1H), 5.62 (s, 1H), 6.50–6.55 (m, 2H), 6.64–6.68 (m, 2H), 7.47 (dd, 1H, J=7.3, 8.3 Hz), 7.52–7.56 (m, 1H), 7.58–7.62 (m, 1H), 7.64 (d, 1H, J=7.3 Hz), 7.84 (d, 1H, J=8.3 Hz), 7.92 (d, 1H, J=8.3 Hz), 8.32 (d, 1H, J=8.3 Hz). ^{13}C NMR ($CDCl_3$) δ 26.8 (q), 55.5 (q), 66.1 (d), 114.5 (d), 114.7 (d), 122.9 (d), 125.6 (d), 125.9 (d), 126.6 (d), 126.8 (d), 129.0 (d), 129.2 (d), 131.2 (s), 133.9 (s), 134.2 (s), 140.7 (s), 152.1 (s), 204.8 (s). Anal. Calcd for $C_{20}H_{19}NO_2$: C, 78.66%; H, 6.27%; N, 4.59%. Found: C, 78.53%; H, 6.19%; N, 4.50%.

*4.3.11. 4-(1-(4-Methoxyphenylamino)-2-oxopropyl)-benzonitrile (**2k**)*

Pale yellow paste. R_f 0.45 (hexanes/ethyl acetate=2/1). IR (neat) 3377, 2230, 1721, 1605, 1514, 824, 758 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 2.14 (s, 3H), 3.69 (s, 3H), 5.00 (s, 1H), 5.19 (br s, 1H), 6.42–6.46 (m, 2H), 6.67–6.71 (m, 2H), 7.59–7.62 (m, 2H), 7.67–7.70 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 26.6 (q), 55.4 (q), 68.4 (d), 112.0 (s), 114.3 (d), 114.7 (d), 118.2 (s), 128.4 (d), 132.7 (d), 139.3 (s), 143.8 (s), 152.3 (s), 202.4 (s). Anal. Calcd for $C_{17}H_{18}N_2O_2$: C, 72.84%; H, 5.75%; N, 9.99%. Found: C, 72.65%; H, 5.84%; N, 10.18%.

*4.3.12. Methyl 5-(4-methoxyphenylamino)-4-oxo-5-phenylpentanoate (**2l**)*

Pale yellow paste. R_f 0.25 (hexanes/ethyl acetate=5/1). IR (neat) 3383, 1732, 1605, 1514, 822, 764, 702 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.42–2.50 (m, 1H), 2.56–2.67 (m, 2H), 2.80–2.89 (m, 1H), 3.63 (s, 3H), 3.69 (s, 3H), 5.01 (s, 1H), 5.11 (br s, 1H), 6.49–6.54 (m, 2H), 6.68–6.72 (m, 2H), 7.30–7.34 (m, 1H), 7.36–7.40 (m, 2H), 7.44–7.48 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 27.6 (t), 33.7 (t), 51.5 (q), 55.4 (q), 68.3 (d), 114.3 (d), 114.5 (d), 127.6 (d), 128.1 (d), 129.0 (d), 138.0 (s), 140.1 (s), 152.0 (s), 172.5 (s), 205.0 (s). Anal. Calcd for $C_{19}H_{21}NO_4$: C, 69.71%; H, 6.47%; N, 4.28%. Found: C, 69.78%; H, 6.41%; N, 4.22%.

*4.3.13. Methyl 5-(4-methoxyphenyl)-5-(4-methoxyphenylamino)-4-oxopentanoate (**2m**)*

Pale yellow paste. R_f 0.33 (hexanes/ethyl acetate=2/1). IR (neat) 3381, 1732, 1717, 1609, 1514, 824 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.41–2.50 (m, 1H), 2.56–2.68 (m, 2H), 2.78–2.87 (m, 1H), 3.64 (s, 3H), 3.70 (s, 3H), 3.80 (s, 3H), 4.95 (s, 1H), 5.06 (br s, 1H), 6.49–6.53 (m, 2H), 6.68–6.72 (m, 2H), 6.89–6.93 (m, 2H), 7.34–7.38 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 27.6 (t), 33.7 (t), 51.6 (q), 55.0 (q), 55.4 (q), 67.6 (d), 114.36 (d), 114.41 (d), 114.6 (d), 128.8 (d), 129.8 (s), 140.2 (s), 152.0 (s), 159.4 (s), 172.6 (s), 205.4 (s). Anal. Calcd for $C_{20}H_{23}NO_5$: C, 67.21%; H, 6.49%; N, 3.92%. Found: C, 67.43%; H, 6.56%; N, 3.87%.

*4.3.14. Methyl 5-(2-methoxyphenyl)-5-(4-methoxyphenylamino)-4-oxopentanoate (**2n**)*

Pale yellow paste. R_f 0.33 (hexanes/ethyl acetate=2/1). IR (neat) 3393, 1738, 1720, 1618, 1599, 1514, 1489, 822, 758, 733 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.43–2.51 (m, 1H), 2.57–2.66 (m, 2H), 2.81–2.91 (m, 1H), 3.63 (s, 3H), 3.69 (s, 3H), 3.99 (s, 3H), 5.05 (br s, 1H), 5.54 (s, 1H), 6.49–6.53 (m, 2H), 6.67–6.71 (m, 2H), 6.29 (t, 1H, J=7.3 Hz), 6.97 (d, 1H, J=8.3 Hz), 7.25–7.30 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 27.5 (t), 33.5 (t), 51.4 (q), 55.28 (q), 55.31 (q), 60.9 (d), 110.7 (d), 114.0 (d), 114.4 (d), 121.0 (d), 126.0 (s), 128.0 (d), 129.1 (q), 140.3 (s), 151.8 (s), 156.7 (s), 172.6 (s), 205.1 (s). Anal. Calcd for $C_{20}H_{23}NO_5$: C, 67.21%; H, 6.49%; N, 3.92%. Found: C, 67.35%; H, 6.58%; N, 3.93%.

*4.3.15. Methyl 5-(3,4-dimethoxyphenyl)-5-(4-methoxyphenylamino)-4-oxopentanoate (**2o**)*

Pale yellow paste. R_f 0.20 (hexanes/ethyl acetate=2/1). IR (neat) 3375, 1732, 1593, 1514, 824, 766, 733 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.41–2.51 (m, 1H), 2.57–2.69 (m, 2H), 2.80–2.88 (m, 1H), 3.64 (s, 3H), 3.70 (s, 3H), 3.86 (s, 3H), 3.88 (s, 3H), 4.93 (s, 1H), 5.06 (br s, 1H), 6.51–6.55 (m, 2H), 6.69–6.72 (m, 2H), 6.87–6.89 (m, 2H), 7.05–7.08 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 27.7 (t), 33.6 (t), 51.6 (q), 55.4 (q), 55.7 (q), 68.1 (d), 109.9 (d), 111.3 (d), 114.4 (d), 114.6 (d), 120.4 (d), 130.4 (s), 140.3 (s), 148.9 (s), 149.5 (s), 152.0 (s), 172.6 (s), 205.4 (s). Anal. Calcd for $C_{21}H_{25}NO_6$: C, 65.10%; H, 6.50%; N, 3.62%. Found: C, 65.23%; H, 6.60%; N, 3.65%.

*4.3.16. Methyl 5-(4-fluorophenyl)-5-(4-methoxyphenylamino)-4-oxopentanoate (**2p**)*

Pale yellow paste. R_f 0.37 (hexanes/ethyl acetate=2/1). IR (neat) 3385, 1736, 1603, 1514, 824 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.44–2.52 (m, 1H), 2.55–2.70 (m, 2H), 2.79–2.87 (m, 1H), 3.64 (s, 3H), 3.70 (s, 3H), 5.00 (s, 1H), 5.10 (br s, 1H), 6.47–6.51 (m, 2H), 6.68–6.72 (m, 2H), 7.05–7.11 (m, 2H), 7.42–7.47 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 27.7 (t), 33.8 (t), 51.7 (q), 55.5 (q), 67.6 (d), 114.5 (d), 114.7 (d), 116.1 (d, J_{CCF}= 22.1 Hz), 129.4 (d, J_{CCCF}=7.7 Hz), 133.9 (s, J_{CCCCF}=2.9 Hz), 140.0 (s), 152.2 (s), 162.5 (s, J_{CF}=247.6 Hz), 172.6 (s), 204.9 (s). Anal. Calcd for $C_{19}H_{20}FNO_4$: C, 66.08%; H, 5.84%; N, 4.06%. Found: C, 66.14%; H, 5.80%; N, 3.96%.

*4.3.17. Methyl 5-(4-methoxyphenylamino)-5-(naphthalen-1-yl)-4-oxopentanoate (**2q**)*

Pale yellow paste. R_f 0.47 (hexanes/ethyl acetate=2/1). IR (neat) 3387, 1717, 1618, 1597, 1514, 822, 800, 779, 735 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.35–2.44 (m, 2H), 2.60–2.67 (m, 1H), 2.81–2.90 (m, 1H), 3.61 (s, 3H), 3.67 (s, 3H), 5.20 (br s, 1H), 5.70 (s, 1H), 6.52–6.55 (m, 2H), 6.65–6.69 (m, 2H), 7.46–7.51 (m, 1H), 7.53–7.57 (m, 1H), 7.58–7.63 (m, 1H), 7.64–7.68 (m, 1H), 7.85 (d, 1H, J=8.3 Hz), 7.92 (d, 1H, J=8.3 Hz), 8.32 (d, 1H, J=8.7 Hz). ^{13}C NMR ($CDCl_3$) δ 27.5 (t), 33.8 (t), 51.4 (q), 55.3 (q), 65.5 (d), 114.4 (d), 114.5 (d), 122.8 (d), 125.5 (d), 125.8 (d), 126.7 (d), 128.9 (d), 129.0 (d), 131.1 (s), 133.7 (s), 134.1 (s), 140.6 (s), 152.0 (s), 172.5 (s), 205.7 (s). Anal. Calcd for $C_{23}H_{23}NO_4$: C, 73.19%; H, 6.14%; N, 3.71%. Found: C, 73.04%; H, 6.09%; N, 3.65%.

*4.3.18. Methyl 6-(4-methoxyphenylamino)-5-oxo-6-phenylhexanoate (**2r**)*

Pale yellow paste. R_f 0.43 (hexanes/ethyl acetate=5/1). IR (neat) 3354, 1734, 1599, 1514, 826, 756, 702 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.73–1.90 (m, 2H), 2.10–2.26 (m, 2H), 2.42–2.60 (m, 2H), 3.60 (s, 3H), 3.68 (s, 3H), 4.94 (s, 1H), 5.13 (br s, 1H), 6.48–6.52 (m, 2H), 6.67–6.70 (m, 2H), 7.28–7.32 (m, 1H), 7.34–7.38 (m, 2H), 7.40–7.44 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 18.7 (t), 32.5 (t), 37.8 (t), 51.4 (q), 55.5 (q), 68.4 (d), 114.4 (d), 114.7 (d), 127.7 (d), 128.2 (d), 129.1 (d), 138.0 (s), 140.1 (s), 152.0 (s), 173.2 (s), 205.9 (s). Anal. Calcd for $C_{20}H_{23}NO_4$: C, 70.36%; H, 6.79%; N, 4.10%. Found: C, 70.48%; H, 6.83%; N, 3.99%.

*4.3.19. Methyl 2-(4-methoxyphenylamino)-2-phenylacetate (**3a**)*

White solid. Mp 107–108 °C. R_f 0.4 (hexanes/ethyl acetate=5/1). IR (KBr) 3418, 1732, 1620, 1597, 1585, 1514, 989, 939, 818, 764, 731, 698 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.71 (s, 3H), 3.73 (s, 3H), 4.67 (br s, 1H), 5.02 (s, 1H), 6.51–6.55 (m, 2H), 6.70–6.74 (m, 2H), 7.28–7.39 (m, 3H), 7.46–7.50 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 52.6 (q), 55.5 (q), 61.5 (d), 114.6 (d), 114.7 (d), 127.1 (d), 128.1 (d), 128.7 (d), 137.6 (s), 140.0 (s), 152.3 (s), 172.4 (s). Anal. Calcd for $C_{16}H_{17}NO_3$: C, 70.83%; H, 6.32%; N, 5.16%. Found: C, 70.85%; H, 6.32%; N, 5.23%.

4.3.20. Methyl 2-(4-methoxyphenyl)-2-(4-methoxyphenylamino)acetate (**3b**)

White solid. Mp 91–92 °C. R_f 0.3 (hexanes/ethyl acetate=5/1). IR (KBr) 3366, 1728, 1612, 1512, 972, 824, 797, 752, 704 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.71 (s, 3H), 3.72 (s, 3H), 3.79 (s, 3H), 4.60 (br s, 1H), 4.96 (s, 1H), 6.51–6.55 (m, 2H), 6.70–6.75 (m, 2H), 6.86–6.90 (2H), 7.38–7.41 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 52.5 (q), 55.1 (q), 55.5 (q), 60.8 (d), 114.1 (d), 114.6 (d), 114.7 (d), 128.3 (d), 129.6 (s), 140.1 (s), 152.3 (s), 159.4 (s), 172.7 (s). Anal. Calcd for $C_{17}H_{19}NO_4$: C, 67.76%; H, 6.36%; N, 4.65%. Found: C, 67.58%; H, 6.30%; N, 4.67%.

4.3.21. Methyl 2-(2-methoxyphenyl)-2-(4-methoxyphenylamino)acetate (**3c**)

White solid. Mp 123–124 °C. R_f 0.25 (hexanes/ethyl acetate=5/1). IR (KBr) 3387, 1736, 1601, 1518, 1497, 974, 827, 773, 756 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.70 (s, 3H), 3.71 (s, 3H), 3.91 (s, 3H), 4.61 (br s, 1H), 5.44 (s, 3H), 6.58–6.63 (m, 2H), 6.70–6.74 (m, 2H), 6.91–6.95 (m, 2H), 7.25–7.30 (m, 1H), 7.33–7.35 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 52.2 (q), 55.3 (q), 55.5 (q and t), 110.9 (d), 114.5 (d), 114.8 (d), 120.8 (d), 126.3 (s), 127.9 (d), 129.2 (d), 140.4 (s), 152.3 (s), 156.9 (s), 172.8 (s). Anal. Calcd for $C_{17}H_{19}NO_4$: C, 67.76%; H, 6.36%; N, 4.65%. Found: C, 67.79%; H, 6.36%; N, 4.61%.

4.3.22. Methyl 2-(3,4-dimethoxyphenyl)-2-(4-methoxyphenylamino)acetate (**3d**)

Pale yellow paste. R_f 0.4 (hexanes/ethyl acetate=2/1). IR (neat) 3369, 1740, 1593, 1514, 824, 764 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.71 (s, 3H), 3.73 (s, 3H), 3.87 (s, 3H), 3.88 (s, 3H), 4.60 (br s, 1H), 4.94 (s, 1H), 6.52–6.57 (m, 2H), 6.70–6.75 (m, 2H), 6.84 (d, 1H, J=8.3 Hz), 6.99 (d, 1H, J=1.8 Hz), 7.03 (dd, 1H, J=1.8, 8.3 Hz). ^{13}C NMR ($CDCl_3$) δ 52.3 (q), 55.2 (q), 55.5 (q), 61.0 (d), 109.8 (d), 110.9 (d), 114.5 (d), 119.4 (d), 129.9 (s), 140.0 (s), 148.6 (s), 148.9 (s), 152.2 (s), 172.4 (s). Anal. Calcd for $C_{18}H_{21}NO_5$: C, 65.24%; H, 6.39%; N, 4.23%. Found: C, 65.40%; H, 6.31%; N, 4.10%.

4.3.23. Methyl 2-(4-fluorophenyl)-2-(4-methoxyphenylamino)acetate (**3e**)

White solid. Mp 99–100 °C. R_f 0.35 (hexanes/ethyl acetate=5/1). IR (KBr) 3418, 1734, 1601, 1516, 837, 818, 806, 773 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.71 (s, 3H), 3.73 (s, 3H), 4.67 (br s, 1H), 4.99 (s, 1H), 6.49–6.53 (m, 2H), 6.70–6.74 (m, 2H), 7.01–7.06 (m, 2H), 7.44–7.49 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 52.7 (q), 55.5 (q), 60.8 (d), 114.7 (d), 115.6 (d, J_{CCF}=21.9 Hz), 128.8 (d, J_{CCCF}=7.6 Hz), 133.4 (s, J_{CCCCF}=2.9 Hz), 139.8 (s), 152.5 (s), 162.4 (s, J_{CF}=245.1 Hz), 172.3 (s). Anal. Calcd for $C_{16}H_{16}FNO_3$: C, 66.43%; H, 5.57%; N, 4.84%. Found: C, 66.42%; H, 5.53%; N, 4.80%.

4.3.24. Methyl 2-(4-methoxyphenylamino)-2-(naphthalen-1-yl)acetate (**3f**)

Pale yellow paste. R_f 0.35 (hexanes/ethyl acetate=5/1). IR (neat) 3398, 1732, 1618, 1597, 1514, 822, 799, 777, 735 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.69 (s, 3H), 3.71 (s, 3H), 4.71 (br s, 1H), 5.78 (s, 1H), 6.52–6.56 (m, 2H), 6.69–6.73 (m, 2H), 7.44 (dd, 1H, J=7.3, 8.3 Hz), 7.52–7.55 (m, 1H), 7.57–7.61 (m, 1H), 7.62–7.64 (m, 1H), 7.83 (d, 1H, J=8.3 Hz), 7.89–7.92 (m, 1H), 8.30 (d, 1H, J=8.3 Hz). ^{13}C NMR ($CDCl_3$) δ 52.5 (q), 55.4 (q), 58.1 (d), 114.4 (d), 114.7 (d), 123.2 (d), 124.9 (d), 125.4 (d), 125.7 (d), 126.5 (d), 128.8 (d), 128.9 (d), 131.1 (s), 133.4 (s), 133.9 (s), 140.3 (s), 152.4 (s), 172.7 (s). Anal. Calcd for $C_{20}H_{19}NO_3$: C, 74.75%; H, 5.96%; N, 4.36%. Found: C, 74.86%; H, 5.76%; N, 4.19%.

4.3.25. Methyl 2-(furan-2-yl)-2-(4-methoxyphenylamino)acetate (**3h**)

White solid. Mp 80–81 °C. R_f 0.4 (hexanes/ethyl acetate=5/1). ^1H NMR ($CDCl_3$) δ 3.73 (s, 3H), 3.77 (s, 3H), 4.50 (br s, 1H), 5.15 (s, 1H), 6.33–6.37 (m, 1H), 6.60–6.65 (m, 2H), 6.74–6.79 (m, 2H), 6.90–6.95 (m, 1H), 7.38–7.41 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 52.7 (q), 55.4 (q), 56.0 (d), 108.0 (d), 110.5 (d), 114.7 (d), 115.2 (d), 139.7 (s), 142.6 (d), 150.1 (s), 152.9 (s), 170.6 (s). Anal. Calcd for $C_{14}H_{15}NO_4$: C, 64.36%; H, 5.79%; N, 5.36%. Found: C, 64.37%; H, 5.76%; N, 5.33%.

4.4. Typical procedure of formylation and oxidation with CAN of **2** and **3**

A solution of **3a** (100 mg, 0.37 mmol), acetic anhydride (1 mL), and formic acid (3 mL) was refluxed for 2 h. The solution was diluted with 2 M $NaHCO_3$ (50 mL) and extracted with ethyl acetate. After the solvent was removed, the crude formate was dissolved in CH_3CN (5 mL). To the solution was added slowly an aqueous solution (3 mL) of CAN (405 mg, 0.74 mmol) at 5 °C for 1 h. The mixture was diluted with H_2O (30 mL) and extracted with ethyl acetate. After the solvent was removed, the crude mixture was purified by column chromatography on basic alumina (hexanes/ethyl acetate=2/1) to give **5a** in 70% yield.

4.4.1. N-(2-Oxo-1-phenylpropyl)formamide (**4a**)

Colorless paste. R_f 0.25 (hexanes/ethyl acetate=1/1). ^1H NMR ($CDCl_3$) δ 2.12 (s, 3H), 5.62 (d, 1H, J=6.9 Hz), 7.05 (br s, 1H), 7.31–7.41 (m, 5H), 8.21 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ 26.9 (q), 62.2 (d), 127.8 (d), 128.7 (d), 129.2 (d), 135.8 (s), 160.3 (d), 202.8 (s). Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78%; H, 6.26%; N, 7.90%. Found: C, 67.84%; H, 6.31%; N, 7.69%.

4.4.2. N-(3-Methyl-2-oxo-1-phenylbutyl)formamide (**4d**)

Colorless paste. R_f 0.45 (hexanes/ethyl acetate=1/1). ^1H NMR ($CDCl_3$) δ 0.89 (d, 3H, J=6.9 Hz), 1.16 (d, 3H, J=6.9 Hz), 2.66–2.75 (m, 1H), 5.77 (d, 1H, J=6.9 Hz), 7.09 (br s, 1H), 7.29–7.39 (m, 5H), 8.19 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ 17.8 (q), 19.1 (q), 37.6 (d), 59.9 (d), 128.1 (d), 128.6 (d), 129.1 (d), 135.9 (s), 160.1 (d), 209.3 (s). Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22%; H, 7.37%; N, 6.82%. Found: C, 70.28%; H, 7.33%; N, 6.67%.

*4.4.3. Methyl 2-formamido-2-phenylacetate (**5a**)*

Colorless paste. R_f 0.25 (hexanes/ethyl acetate=1/1). ^{1}H NMR ($CDCl_3$) δ 3.73 (s, 3H), 5.66 (d, 1H, J=7.5 Hz), 6.93 (br s, 1H), 7.31–7.38 (m, 5H), 8.21 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ 52.8 (q), 55.0 (d), 127.1 (d), 128.6 (d), 128.9 (d), 136.0 (s), 160.3 (d), 170.9 (s). Anal. Calcd for $C_{10}H_{11}NO_3$: C, 62.17%; H, 5.74%; N, 7.25%. Found: C, 62.25%; H, 5.73%; N, 7.19%.

*4.4.4. Methyl 2-(4-fluorophenyl)-2-formamidoacetate (**5e**)*

Colorless paste. R_f 0.2 (hexanes/ethyl acetate=1/1). ^{1}H NMR ($CDCl_3$) δ 3.76 (s, 3H), 5.64 (d, 1H, J=7.2 Hz), 6.73 (br s, 1H), 7.03–7.08 (m, 2H), 7.33–7.37 (m, 2H), 8.24 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ 53.0 (q), 54.3 (d), 115.9 (d, J_{CCF}= 22.1 Hz), 128.9 (d, J_{CCCF}=8.6 Hz), 131.9 (s, J_{CCCCF}=3.8 Hz), 160.2 (s), 162.7 (s, J_{CF}=247.6 Hz), 170.8 (s). Anal. Calcd for $C_{10}H_{10}FNO_3$: C, 56.87%; H, 4.77%; N, 6.63%. Found: C, 56.75%; H, 4.83%; N, 6.50%.

References and notes

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