Tetrahedron 64 (2008) 11034–11040

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

One-pot three-component reaction providing 1,5-benzodiazepine derivatives

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ARTICLE INFO

Article history:
Received 8 August 2008
Received in revised form
25 September 2008
Accepted 25 September 2008
Available online 7 October 2008

ABSTRACT

The novel one-pot three-component reaction of aromatic aldehydes, 1,2-phenylenediamine, and β-keto esters is described. This reaction involves the γ-selective C–C bond formation of β-keto esters and produces 1,5-benzodiazepine derivatives.

1. Introduction

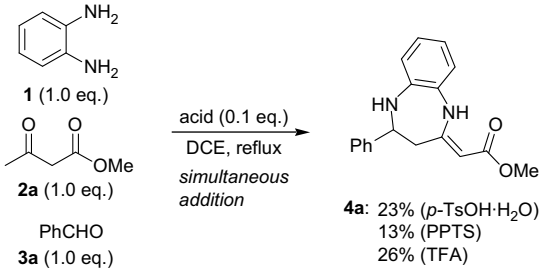
1,5-Benzodiazepines are some of the important heterocyclic compounds from the viewpoint of biological activities.[1] General methods for preparing these compounds include the condensations of 1,2-phenylenediamine with α,β-unsaturated carbonyl compounds or β-haloketones.[2] As the condensation partners, ketones were also used;[3] in this case, 1,2-phenylenediamine and 2 equiv of ketones were condensed through an intramolecular imine–enamine cyclization. Instead of 1,2-phenylenediamine, *o*-nitrophenylazide and *o*-nitroaniline were used in the presence of a reducing reagent such as SmI_2 and $TiCl_4/Sm$.[4] In addition, the condensation of aldehdyes with enamines prepared from 1,2-phenylenediamine was also reported.[1h,5] Although these methods were useful and the products from each method were not similar, it is desirable to develop the reaction readily providing divergent 1,5-benzodiazepine derivatives.

Recently, multi-component reactions have been receiving more and more attention because of their efficiency and diversity of products.[6] Their utilities were fully realized in the process of drug discovery[7] and the total synthesis of complex natural products.[8] Although a great number of such useful reactions have been reported, the development of a novel multi-component reaction is still important in the fields of medicinal and organic syntheses.

We have recently reported the novel three-component reaction of aromatic aldehydes, ethylenediamine, and β-keto esters producing seven-membered 1,4-azepane compounds.[9,10] This reaction is very unique because β-keto esters react at the generally unreactive γ-positions. The reaction mechanism is rationalized as follows. During the first stage of the reaction, ethylenediamine bridges the aldehyde and the β-ketoesters to form the intermediates involving imines and enamino esters. Next, the intramolecular reaction of the intermediate occurs between the imine and γ-position of the enamino ester. In this paper, we describe the one-pot three-component reaction providing 1,5-benzodiazepine derivatives using 1,2-phenylenediamine in our reaction instead of ethylenediamine.

2. Results and discussion

The reaction was first examined in detail using 1,2-phenylenediamine (**1**), methyl acetoacetate (**2a**), and benzaldehyde (**3a**). When all substrates were simultaneously added to *p*-TsOH, similar to the previous procedure, the desired product **4a**, the γ-addition product, was obtained, though the yield was low. Reactions with the other acids did not improve the yield (Scheme 1).



Scheme 1. First attempts.

It was considered that the formation of the intermediate **i** involving imines and enamino esters was important for producing **4a** in a good yield (Scheme 2). In the case of 1,2-phenylenediamine (**1**), methyl acetoacetate (**2a**), and benzaldehyde (**3a**), the imine intermediate **ii** was first formed from 1,2-phenylenediamine (**1**) and benzaldehyde (**3a**). If the intermediate **i** was formed from the imine intermediate **ii** with methyl acetoacetate (**2a**), the desired reaction would proceed. However, the formation of the intermediate **i**

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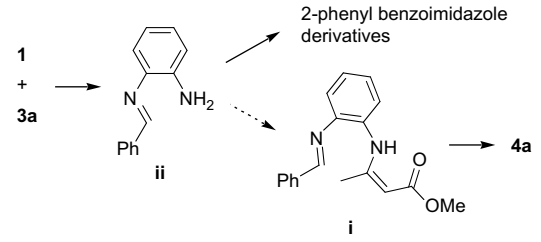
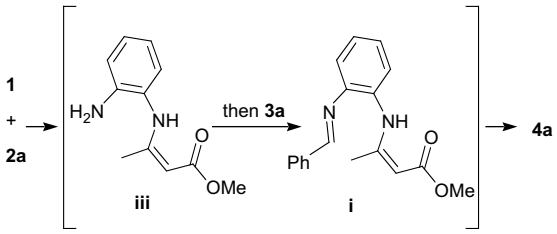
doi:10.1016/j.tet.2008.09.076

seemed to be much slower than the intramolecular cyclization of the amine to the imine unit of intermediate **ii**. It is well known that in the presence of acid catalysts the condensations of 1,2-phenylenediamine (**1**) and aldehydes produced the benzoimidazole derivatives.[11] Actually, the formation of 2-phenyl benzoimidazole and *N*-benzyl 2-phenyl benzoimidazole was confirmed in this reaction.



Scheme 2. Reaction of intermediate **ii**.

Therefore, we modified the reaction procedure to form the intermediate **i**. Thus, 1,2-phenylenediamine (**1**) and methyl acetoacetate (**2a**) were first condensed to form the enamino ester intermediate **iii**, and benzaldehyde (**3a**) was added to the intermediate **iii** to form intermediate **i** (Scheme 3).



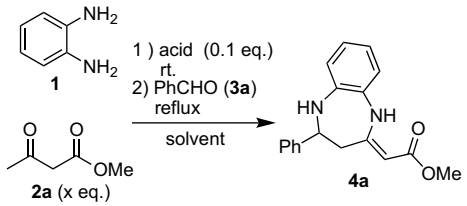
Scheme 3. Modification of reaction procedure.

As we expected, the modification of the reaction procedure improved the yield of the product (Table 1, entry 1). Various conditions concerning the ratio of the reagent, solvent, and acid were next tested using the improved procedure. Some of the results are shown in Table 1. The appropriate ratio of the reagents was first determined. When an equimolar amount of 1,2-phenylenediamine (**1**) and benzaldehyde (**3a**) were used, the reaction with 1.2 equiv of methyl acetoacetate (**2a**) gave better results (Table 1, entries 1–3). Based on the results of the reactions in various solvents (DCE, toluene, MeOH, CH_3CN, THF, CH_2Cl_2, $CHCl_3$, and $PhCF_3$), DCE appeared to be the best solvent (Table 1, entries 2 and 4–10). As the result of having examined various acids (TFA, TsOH, TfOH, AcOH, $PhPO_3H$, Cl_3CCO_2H, *p*-$NO_2C_6H_4CO_2H$, $C_6F_5CO_2H$, $Zn(OTf)_2$, $Yb(OTf)_3$, and $Cu(BF_4)_2$), $C_6F_5CO_2H$ appeared to give the best results.[12] The additions of molecular sieves 4 Å or $MgSO_4$ were not effective. Finally, the ratio of the substrate and reagent was examined once again and it was concluded that 1.0 equiv of 1,2-phenylenediamine (**1**) and benzaldehyde (**3a**), 1.3 equiv of methyl acetoacetate (**2a**), and 0.2 equiv of $C_6F_5CO_2H$ gave the best results (Table 2, entry 1).

We then applied the optimized conditions to the synthesis of the 1,5-benzodiazepine derivatives from various aromatic aldehydes using 1,2-phenylenediamine (**1**) and methyl acetoacetate (**2a**) (Table 2). At first, various benzaldehydes having the substituent at the *para* position were examined. Although electron-withdrawing groups gave much better results, both the electron-donating and electron-withdrawing groups gave moderate yields (Table 2, entries 2–7). The result of using *o*-methyl benzaldehyde (**3j**) indicated that this reaction was more influenced by steric effects (Table 2, entry 10). It is worth mentioning that esters and nitriles are tolerant under the optimized conditions (Table 2, entries 6 and 7). Furthermore, not only various substituted benzaldehydes (**3a**–**3k**), but also 2-naphthaldehyde (**3l**), 3-furancarboxaldehyde (**3m**), and 2-thiophenecarboxaldehyde (**3n**) were applicable (Table 2, entries 12–14).

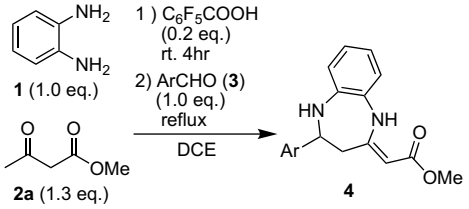
Various β-keto esters were next examined using 1,2-phenylenediamine (**1**) and benzaldehyde (**3a**) (Table 3). Not only benzyl acetoacetate (**2b**), but also *tert*-butyl acetoacetate (**2c**) having the acid sensitive *tert*-butyl ester moiety was tolerant and gave good results (Table 3, entries 1 and 2). Unfortunately, the reaction using

Table 1
Optimization



Entry	Acid	Solvent	*x* equiv	Yield (%)
1	TFA	DCE	1.0	37
2	TFA	DCE	1.2	54
3	TFA	DCE	1.5	47
4	TFA	Toluene	1.2	Complex
5	TFA	MeOH	1.2	Complex
6	TFA	CH_3CN	1.2	38
7	TFA	THF	1.2	40
8	TFA	CH_2Cl_2	1.2	41
9	TFA	$CHCl_3$	1.2	48
10	TFA	$PhCF_3$	1.2	34
11	TsOH	DCE	1.2	27
12	TfOH	DCE	1.2	28
13	$C_6F_5CO_2H$	DCE	1.2	60

Table 2
Reactions with various aldehydes



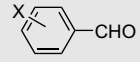
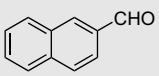
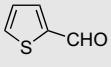
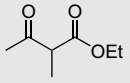
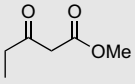
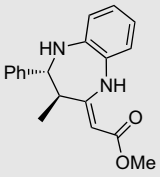
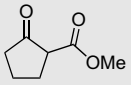
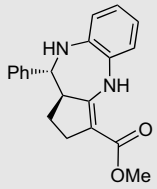
Entry	ArCHO		Yield (%)
			
1	X=H	(**3a**)	**4a**: 68
2	X=*p*-MeO	(**3b**)	**4b**: 57
3	X=*p*-Cl	(**3c**)	**4c**: 66
4	X=*p*-Br	(**3d**)	**4d**: 66
5	X=*p*-NO2	(**3e**)	**4e**: 61
6	X=*p*-CN	(**3f**)	**4f**: 59
7	X=*p*-CO2Me	(**3g**)	**4g**: 57
8	X=*m*-MeO	(**3h**)	**4h**: 54
9	X=*m*-Cl	(**3i**)	**4i**: 58
10	X=*o*-Me	(**3j**)	**4j**: 34
11	X=*o*-Cl	(**3k**)	**4k**: 51
12		(**3l**)	**4l**: 57
13		(**3m**)	**4m**: 33
14		(**3n**)	**4n**: 55

Table 3
Reactions with various β-keto esters

Entry	β-Keto ester (**2**)	Product (**4**)	Yield (%)
1[a]	R=Bn (**2b**)	R=Bn (**4o**)	67
2[a]	R=*t*-Bu (**2c**)	R=*t*-Bu (**4p**)	73
3	 **(2d)**	—	—
4[b]	 **(2e)**	 **(4q)**	16
5[b]	 **(2f)**	 **(4r)**	50

[a] Reactions were carried out under the same condition as Table 2.
[b] First step of reaction was carried out at 50 °C. For details, see Section 4.

ethyl 2-methylacetoacetate (**2d**) did not work, because of a difficulty in preparation of enamino ester, the intermediate of the reaction (Table 3, entry 3).[13] Although the reaction using methyl propionylacetate (**2e**) formed the enamino ester, the yield was low (Table 3, entry 4). On the other hand, methyl 2-oxocyclopentanecarboxylate (**2f**) produced desired compound **4r** in a moderate yield (Table 3, entry 5).[14] The reaction was considered to proceed through the formation of the intermediate **i** (Scheme 3) and γ-addition probably occurred via the corresponding diene form. Thus the decrease in the yield of the β-keto ester (**2e**) was probably due to the 1,3-allylic strain of the *Z*-enolate of the diene form for intramolecular γ-addition. This indicates that the easy formation of the diene intermediate is essential for this transformation.

Lastly, we did several experiments examining the γ-selectivity. In a previous paper, the related reaction using the enamino ester, which was prepared from 1,2-phenylenediamine (**1**) and ethyl acetoacetate, was reported.[1h] Thus the enamino ester and *m*-nitrobenzaldehyde were treated with acetic acid in ethanol at rt to produce the 1,5-benzodiazepine derivative via the addition at the α-position of the enamino ester. Only one substrate was reported in the paper, and the regioselectivity of the reaction of the enamino ester was distinct from our results. Therefore, we were very interested in the differences in the selectivity, thus the following experiments with the enamino ester **5** were carried. The solvent effect was first investigated. When **5** and *p*-chlorobenzaldehyde (**3c**) were treated with $C_6F_5CO_2H$ in refluxing DCE, the γ-adduct **4c** was selectively obtained (Table 4, entry 1). At rt, the α-addition was confirmed, but the major product was the γ-adduct **4c** (γ/α=89:11) (Table 4, entry 2). On the other hand, when EtOH was used as the solvent, only the α-adduct **6** was obtained (Table 4, entry 3). The α-selectivity was also observed in aprotic solvents such as CH_3CN (γ/α=31:69) and THF (γ/α=1<:99) (Table 4, entries 4 and 5). These results showed that the polarity of the solvent was more important because the protic EtOH and aprotic THF gave the same selectivity.

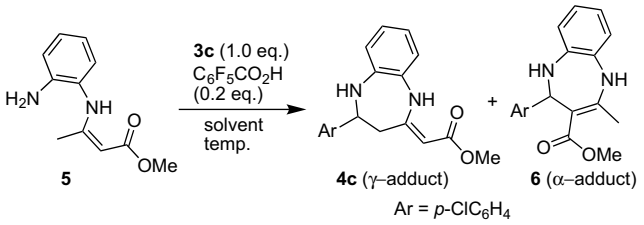
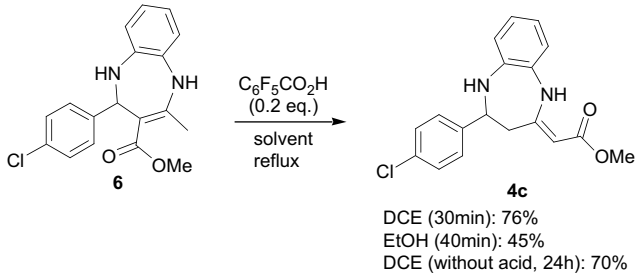


Table 4
Solvent effect

Entry	Solvent	Temperature	Time (h)	Ratio[a] (γ/α)	Yield %[b] (**4c**, **6**)
1	DCE	Reflux	2.5	99:<1	59, —
2	DCE	rt	19	89:11	48, —
3	EtOH	rt	1	<1:99	—, 78
4	CH_3CN	rt	17	31:69	19, 45
5	THF	rt	6	<1:99	—, 70

[a] Ratio was determined from ^{1}H NMR analysis of crude reaction mixtures.
[b] Isolated yield.

The stability of the α-adduct **6** versus the temperature was next tested, because the α-adduct was partially formed in DCE at rt but not under reflux conditions. As shown in Scheme 4, the α-adduct **6** was converted to the γ-adduct **4c** at reflux in DCE in the presence of $C_6F_5CO_2H$. The γ-adduct **4c** was also formed in EtOH, though the yield was lower than that in DCE. Interestingly, the γ-adduct **4c** was formed without the acid catalyst. Based on these results, we considered that the α-adduct **6** was comparatively unstable at higher temperatures and the α-adduct **6** and imine–enaminoester intermediate such as **i** shown in Scheme 3 were both reversible. The γ-adduct **4c**, which seemed to be thermodynamically stable due to the intramolecular hydrogen bonding between NH and C=O functions, was then formed. Accordingly, we now think that the γ-selectivity of the one-pot three-component reaction developed here was mainly due to thermodynamic control. However, further investigations are required, since it was the fact that γ-selectivity was observed in DCE even at rt.



Scheme 4. Effect of the temperature.

3. Conclusion

In conclusion, we have developed a novel one-pot three-component reaction of aromatic aldehydes, 1,2-phenylenediamine, and β-keto esters in the presence of a catalytic acid producing 1,5-benzodiazepine derivatives. The reaction procedure is important for good yields. Thus, the condensations of 1,2-phenylenediamine and the β-keto esters to form the enamino esters were essential.

The main feature of this reaction is the γ-selective C–C bond formation of β-enamino esters probably due to the thermodynamic control derived from intramolecular hydrogen bonding of the enamino esters.

4. Experimental section

4.1. General

The ^{1}H NMR spectra were measured by 300 MHz or 270 MHz spectrometer with tetramethylsilane as the internal standard at 20–25 °C. IR spectra were recorded by a diffuse reflectance measurement of samples dispersed in KBr powder. E. Merck silica gel 60 for column chromatography and E. Merck pre-coated TLC plates, silica gel F_{254}, for preparative thin-layer chromatography were used.

4.2. One-pot three-component reaction

Typical procedure. $C_6F_5CO_2H$ (0.1 mmol) was added to the solution of 1,2-phenylenediamine (**1**, 5 mmol) and β-keto esters (2, 6 mmol) in DCE (5 ml) at rt under N_2 and the reaction mixture was stirred for 4 h. Aldehyde (3, 5 mmol) was added to the solution and the reaction mixture was stirred under reflux. After the completion of the reaction (judged from TLC analysis), the reaction mixture was cooled to rt. Solvent was evaporated in vacuo and residue was purified by SiO_2 column chromatography to afford compound **4**.

4.2.1. Compound *4a*

Reaction was carried out according to the typical procedure with 1,2-phenylenediamine (**1**, 53 mg, 0.492 mmol), methyl acetoacetate (**2a**, 69 μl, 0.639 mmol), benzaldehyde (**3a**, 50 μl, 0.492 mmol), and $C_6F_5CO_2H$ (20.8 mg, 0.098 mmol) in DCE (4.9 ml) to give **4a** (97.8 mg, 68%). Reaction time for reflux was 3 h. Hexane/AcOEt=3:1 was used as eluent for SiO_2 column chromatography. Pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ=10.22 (br s, 1H), 7.35–7.24 (m, 5H), 7.00–6.87 (m, 3H), 6.76 (d, J=7.8 Hz, 1H), 4.83 (dd, J=9.0, 4.2 Hz, 1H), 4.60 (s, 1H), 3.70 (br s, 1H), 3.66 (s, 1H), 2.67 (dd, J=13.8, 9.0 Hz, 1H), 2.54 ppm (dd, J=13.8, 4.2 Hz, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ=170.3, 158.4, 144.5, 137.7, 129.6, 128.6, 127.7, 125.9, 124.8, 122.3, 121.4, 120.6, 83.6, 65.0, 50.2, 40.2 ppm; IR (KBr): 3279, 2249, 1651, 1645, 1614, 1504, 1232, 1163 cm^{-1}; HRMS (EI): calcd for $C_{18}H_{18}N_2O_2$ [M]$^+$: 294.1368, found 294.1344.

4.2.2. Compound *4b*

Reaction was carried out according to the typical procedure with 1,2-phenylenediamine (**1**, 54.5 mg, 0.504 mmol), methyl acetoacetate (**2a**, 71 μl, 0.655 mmol), 4-methoxybenzaldehyde (**3b**, 61 μl, 0.504 mmol), and $C_6F_5CO_2H$ (21.4 mg, 0.10 mmol) in DCE (5.0 ml) to give **4b** (93.6 mg, 57%). Reaction time for reflux was 6 h. Hexane/AcOEt=7:1 and benzene/AcOEt=9:1 was used as eluent for SiO_2 column chromatography. Pale yellow amorphous; ^{1}H NMR (270 MHz, $CDCl_3$): δ=10.13 (br s, 1H), 7.18 (d, J=10.2, 2H), 6.91–6.77 (m, 5H), 6.66 (dd, J=7.8 Hz, 1H), 4.71 (dd, J=8.6, 4.1 Hz, 1H), 4.52 (s, 1H), 3.71 (s, 3H), 3.59 (br s, 1H), 3.59(s, 3H), 2.61–2.41 ppm (m, 2H); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ=171.3, 160.0, 159.6, 138.7, 137.8, 130.6, 128.0, 125.8, 123.3, 122.3, 121.6, 114.8, 84.6, 65.5, 56.2, 51.3, 41.3 ppm; IR (KBr): 3356, 3275, 2949, 2835, 1659, 1589, 1512, 1439, 1254, 1165 cm^{-1}; HRMS (EI): calcd for $C_{19}H_{20}N_2O_3$ [M]$^+$: 324.1474, found 324.1471.

4.2.3. Compound *4c*

Reaction was carried out according to the typical procedure with 1,2-phenylenediamine (**1**, 53 mg, 0.492 mmol), methyl acetoacetate (**2a**, 69 μl, 0.639 mmol), 4-chlorobenzaldehyde (**3c**, 69.2 mg, 0.492 mmol), and $C_6F_5CO_2H$ (20.8 mg, 0.098 mmol) in DCE (4.9 ml) to give **4c** (97.8 mg, 68%). Reaction time for reflux was 2.5 h. Hexane/AcOEt=4:1 was used as eluent for SiO_2 column chromatography. Pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ=10.18 (br s, 1H), 7.32–7.25 (m, 4H), 7.01–6.89 (m, 3H), 6.76 (d, J=5.1 Hz, 1H), 4.84 (dd, J=7.5, 4.5 Hz, 1H), 4.52 (s, 1H), 3.66 (br s, 1H), 3.66 (s, 3H), 2.63–2.49 ppm (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=170.4, 158.0, 142.8, 137.8, 133.5, 130.2, 128.8, 127.6, 125.0, 122.5, 122.0, 120.9, 84.2, 64.4, 50.3, 39.8 ppm; IR (KBr): 3276, 2252, 1655, 1591, 1490, 1234, 1168 cm^{-1}; HRMS (EI): calcd for $C_{18}H_{17}N_2O_2Cl$ [M]$^+$: 328.0978, found 328.0989.

4.2.4. Compound *4d*

Reaction was carried out according to the typical procedure with 1,2-phenylenediamine (**1**, 53.9 mg, 0.498 mmol), methyl acetoacetate (**2a**, 70 μl, 0.647 mmol), 4-bromobenzaldehyde (**3d**, 92.3 mg, 0.497 mmol), and $C_6F_5CO_2H$ (21.2 mg, 0.099 mmol) in DCE (4.9 ml) to give **4d** (122.1 mg, 66%). Reaction time for reflux was 2.5 h. Hexane/AcOEt=12:1 was used as eluent for SiO_2 column chromatography. Pale yellow amorphous; ^{1}H NMR (300 MHz, $CDCl_3$): δ=10.10 (br s, 1H), 7.41–7.36 (m, 2H), 7.20–7.15 (m, 2H), 6.94–6.82 (m, 3H), 6.70 (d, J=7.2 Hz, 1H), 4.76 (dd, J=7.5, 4.5 Hz, 1H), 4.45 (s, 1H), 3.59 (br s, 1H), 3.59 (s, 3H), 2.58–2.42 ppm (m, 2H); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ=170.3, 157.8, 143.2, 137.7, 131.7, 130.2, 127.9, 125.0, 122.4, 122.0, 121.6, 120.9, 84.2, 64.6, 50.4, 39.9 ppm; IR (KBr): 3352, 3282, 2947, 1651, 1589, 1487, 1435, 1232, 1163 cm^{-1}; HRMS (EI): calcd for $C_{18}H_{17}N_2O_2Br$ [M]$^+$: 372.0473, found 372.0449.

4.2.5. Compound *4e*

Reaction was carried out according to the typical procedure with 1,2-phenylenediamine (**1**, 37.4 mg, 0.346 mmol), methyl acetoacetate (**2a**, 49 μl, 0.45 mmol), 4-nitrobenzaldehyde (**3e**, 52.3 mg, 0.346 mmol), and $C_6F_5CO_2H$ (14.7 mg, 0.069 mmol) in DCE (3.5 ml) to give **4e** (71.9 mg, 61%). Reaction time for reflux was 1.5 h. Hexane/AcOEt=4:1 and benzene/AcOEt=50:1 were used as eluent for SiO_2 column chromatography. Pale yellow amorphous; ^{1}H NMR (300 MHz, $CDCl_3$): δ=10.14 (br s, 1H), 8.17 (d, J=8.4 Hz, 2H), 7.59 (d, J=8.4 Hz, 2H), 7.04–6.96 (m, 3H), 6.84 (d, J=7.5 Hz, 1H), 5.04 (m, 1H), 4.40 (s, 1H), 3.79 (br s, 1H), 3.65 (s, 3H), 2.80 (dd, J=13.5, 4.5 Hz, 1H), 2.48 ppm (dd, J=13.8, 6.3 Hz, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ=170.2, 157.4, 151.5, 147.6, 138.2, 130.8, 127.6, 125.3, 123.9, 122.7, 122.5, 121.3, 84.8, 64.7, 50.6, 39.5 ppm; IR (KBr): 3366, 3279, 2949, 2837, 1666, 1634, 1529, 1439, 1352, 1236, 1170, 1117 cm^{-1}; HRMS (EI): calcd for $C_{18}H_{17}N_3O_4$ [M]$^+$: 339.1219, found 339.1221.

4.2.6. Compound *4f*

Reaction was carried out according to the typical procedure with 1,2-phenylenediamine (**1**, 53 mg, 0.492 mmol), methyl acetoacetate (**2a**, 69 μl, 0.639 mmol), 4-formylbenzonitrile (**3f**, 64.5 mg, 0.492 mmol), and $C_6F_5CO_2H$ (20.8 mg, 0.098 mmol) in DCE (4.9 ml) to give **4f** (92.4 mg, 59%). Reaction time for reflux was 2.5 h. Hexane/AcOEt=3:1 was used as eluent for SiO_2 column chromatography. Pale yellow solid; mp 153–155 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=10.12 (br s, 1H), 7.61 (d, J=8.1 Hz, 2H), 7.51 (d, J=8.1 Hz, 2H), 7.02–6.94 (m, 3H), 6.79 (d, J=7.2 Hz, 1H), 5.01–4.91 (m, 1H), 4.40 (s, 1H), 3.69 (br s, 1H), 3.64 (s, 3H), 2.73 (dd, J=13.8, 4.5 Hz, 1H), 2.45 ppm (dd, J=13.8, 6.9 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=170.3, 157.2, 149.2, 137.8, 132.5, 130.5, 127.2, 125.2, 122.6, 122.5, 121.1, 118.7, 111.7, 84.7, 64.7, 50.5, 39.3 ppm; IR (KBr): 3348, 3280, 2947, 2227, 1651, 1614, 1589, 1502, 1267, 1232 cm^{-1}; HRMS (EI): calcd for $C_{19}H_{17}N_3O_2$ [M]$^+$: 319.1321, found 319.1321.

4.2.7. Compound *4g*

Reaction was carried out according to the typical procedure with 1,2-phenylenediamine (**1**, 42.2 mg, 0.390 mmol), methyl acetoacetate (**2a**, 55 μl, 0.507 mmol), methyl 4-formylbenzoate (**3g**, 55 μl, 0.390 mmol), and $C_6F_5CO_2H$ (16.6 mg, 0.078 mmol) in DCE (3.9 ml)

to give **4g** (97.8 mg, 68%). Reaction time for reflux was 3 h. Hexane/AcOEt=5:1 was used as eluent for SiO_2 column chromatography. Pale yellow amorphous; ^{1}H NMR (300 MHz, $CDCl_3$): δ=10.21 (br s, 1H), 7.38 (d, J=8.4 Hz, 2H), 7.06 (d, J=8.4 Hz, 2H), 7.01–6.89 (m, 3H), 6.77 (d, J=7.8 Hz, 1H), 4.85 (dd, J=8.1, 4.5 Hz, 1H), 4.59 (s, 1H), 3.71 (br s, 1H), 3.67 (s, 3H), 2.67–2.51 (m, 2H), 2.30 ppm (s, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ=170.3, 169.3, 158.2, 150.0, 142.0, 137.6, 129.8, 127.1, 124.9, 122.4, 121.8, 121.7, 120.8, 83.9, 64.5, 50.3, 40.1, 21.1 ppm; IR (KBr): 3352, 3279, 3196, 2984, 2947, 2837, 1759, 1651, 1614, 1504, 1435, 1369, 1165 cm^{-1}; HRMS (EI): calcd for $C_{20}H_{20}N_2O_4$ [M]$^+$: 352.1423, found 352.1428.

4.2.8. Compound **4h**

Reaction was carried out according to the typical procedure with 1,2-phenylenediamine (**1**, 48.2 mg, 0.446 mmol), methyl acetoacetate (**2a**, 63 μl, 0.579 mmol), 3-methoxybenzaldehyde (**3h**, 55 μl, 0.446 mmol), and $C_6F_5CO_2H$ (19.0 mg, 0.089 mmol) in DCE (4.5 ml) to give **4h** (78.0 mg, 54%). Reaction time for reflux was 4 h. Hexane/AcOEt=12:1 was used as eluent for SiO_2 column chromatography. Pale yellow amorphous; ^{1}H NMR (300 MHz, $CDCl_3$): δ=10.21 (br s, 1H), 7.28–7.23 (m, 1H), 7.01–6.77 (m, 7H), 4.81 (dd, J=8.7, 4.2 Hz, 1H), 4.61 (s, 1H), 3.78 (s, 3H), 3.72 (br s, 1H), 3.67 (s, 3H), 2.70–2.52 ppm (m, 2H); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ=170.4, 159.7, 158.5, 146.3, 137.8, 129.74, 127.70, 124.9, 122.4, 121.5, 120.7, 118.2, 113.2, 111.6, 83.8, 65.1, 55.2, 50.3, 40.2 ppm; IR (KBr): 3356, 3281, 2947, 2835, 1651, 1587, 1269, 1232, 1165 cm^{-1}; HRMS (EI): calcd for $C_{19}H_{20}N_2O_3$ [M]$^+$: 324.1474, found 324.1472.

4.2.9. Compound **4i**

Reaction was carried out according to the typical procedure with 1,2-phenylenediamine (**1**, 41 mg, 0.379 mmol), methyl acetoacetate (**2a**, 53 μl, 0.493 mmol), 3-chlorobenzaldehyde (**3i**, 43 μl, 0.379 mmol), and $C_6F_5CO_2H$ (16.1 mg, 0.076 mmol) in DCE (3.8 ml) to give **4i** (64.0 mg, 51%). Reaction time for reflux was 3.5 h. Hexane/AcOEt=12:1 was used as eluent for SiO_2 column chromatography. Pale yellow amorphous; ^{1}H NMR (300 MHz, $CDCl_3$): δ=10.19 (br s, 1H), 7.36 (s, 1H), 7.27–7.25 (m, 3H), 7.03–6.90 (m, 3H), 6.80–6.78 (m, 1H), 4.84 (dd, J=6.6, 2.4 Hz, 1H), 4.55 (s, 1H), 3.68 (br s, 1H), 3.67 (s, 3H), 2.58–2.42 ppm (m, 2H); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ=170.3, 157.8, 146.4, 137.6, 134.4, 130.0, 129.9, 128.0, 126.3, 125.0, 124.2, 122.4, 121.9, 120.8, 84.2, 64.6, 50.4, 39.9 ppm; IR (KBr): 3348, 3283, 2945, 2852, 1651, 1614, 1591, 1497, 1477, 1435, 1275, 1232 cm^{-1}; HRMS (EI): calcd for $C_{18}H_{17}N_2O_2Cl$ [M]$^+$: 328.0978, found 328.0986.

4.2.10. Compound **4j**

Reaction was carried out according to the typical procedure with 1,2-phenylenediamine (**1**, 44.8 mg, 0.414 mmol), methyl acetoacetate (**2a**, 58 μl, 0.539 mmol), *o*-tolualdehyde (**3j**, 48 μl, 0.414 mmol), and $C_6F_5CO_2H$ (17.6 mg, 0.083 mmol) in DCE (4.1 ml) to give **4j** (43.4 mg, 34%). Reaction time for reflux was 4 h. Hexane/AcOEt=12:1 was used as eluent for SiO_2 column chromatography. Pale yellow amorphous; ^{1}H NMR (300 MHz, $CDCl_3$): δ=10.26 (br s, 1H), 7.53–7.50 (m, 1H), 7.25–7.16 (m, 3H), 7.02–6.86 (m, 3H), 6.79 (d, J=7.8 Hz, 1H), 5.14 (dd, J=9.0, 3.3 Hz, 1H), 4.61 (s, 1H), 3.69 (br s, 1H), 3.69 (s, 3H), 2.72–2.47 (m, 2H), 2.39 ppm (s, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ=170.5, 159.0, 142.8, 137.9, 133.9, 130.6, 129.0, 127.5, 126.6, 125.6, 125.0, 122.6, 121.0, 120.4, 83.5, 60.0, 50.4, 39.5, 19.3 ppm; IR (KBr): 3360, 3277, 3020, 2947, 1655, 1616, 1489, 1437, 1304, 1283, 1265, 1231, 1163 cm^{-1}; HRMS (EI): calcd for $C_{19}H_{20}N_2O_2$ [M]$^+$: 308.1525, found 308.1531.

4.2.11. Compound **4k**

Reaction was carried out according to the typical procedure with 1,2-phenylenediamine (**1**, 43.7 mg, 0.404 mmol), methyl acetoacetate (**2a**, 57 μl, 0.53 mmol), 2-chlorobenzaldehyde (**3k**, 46 μl, 0.41 mmol), and $C_6F_5CO_2H$ (17.1 mg, 0.081 mmol) in DCE (4.0 ml) to give **4k** (67.1 mg, 51%). Reaction time for reflux was 2.5 h. Hexane/AcOEt=12:1 was used as eluent for SiO_2 column chromatography. Pale yellow amorphous; ^{1}H NMR (300 MHz, $CDCl_3$): δ=10.08 (br s, 1H), 7.70 (d, J=6.6 Hz, 1H), 7.35 (d, J=7.2 Hz, 1H), 7.28–7.18 (m, 2H), 7.02–6.89 (m, 3H), 6.82 (d, J=7.5 Hz, 1H), 5.42–5.38 (m, 1H), 4.47 (s, 1H), 3.68 (br s, 1H), 3.64 (s, 3H), 2.74 (dd, J=13.8, 4.2 Hz, 1H), 2.57 ppm (dd, J=6.9, 13.8 Hz, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ=170.2, 157.9, 141.0, 138.1, 131.5, 130.0, 129.4, 128.7, 127.9, 127.0, 125.0, 122.4, 121.7, 120.7, 84.3, 60.8, 50.3, 37.5 ppm; IR (KBr): 3358, 3277, 3020, 2988, 2947, 1651, 1589, 1504, 1470, 1435, 1270, 1232, 1167 cm^{-1}; HRMS (EI): calcd for $C_{18}H_{17}N_2O_2Cl$ [M]$^+$: 328.0978, found 328.0964.

4.2.12. Compound **4l**

Reaction was carried out according to the typical procedure with 1,2-phenylenediamine (**1**, 53 mg, 0.492 mmol), methyl acetoacetate (**2a**, 69 μl, 0.639 mmol), 2-naphthaldehyde (**3l**, 76.8 mg, 0.492 mmol), and $C_6F_5CO_2H$ (20.8 mg, 0.098 mmol) in DCE (4.9 ml) to give **4l** (96.9 mg, 57%). Reaction time for reflux was 2 h. Hexane/AcOEt=4.5:1 was used as eluent for SiO_2 column chromatography. Pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ=10.25 (br s, 1H), 7.83–7.78 (m, 4H), 7.49–7.44 (m, 3H), 7.01–6.93 (m, 3H), 6.78 (d, J=7.5 Hz, 1H), 4.99 (dd, J=8.4, 4.2 Hz, 1H), 4.60 (s, 1H), 3.78 (br s, 1H), 3.66 (s, 3H), 2.76 (dd, J=13.8, 8.4 Hz, 1H), 2.61 ppm (dd, J=13.8, 4.2 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=170.5, 158.6, 141.9, 137.9, 133.2, 133.0, 129.9, 128.7, 127.9, 127.6, 126.3, 126.0, 125.1, 124.8, 124.1, 122.5, 121.7, 120.9, 83.9, 65.2, 50.3, 39.9 ppm; IR (KBr): 3277, 3057, 2250, 1654, 1627, 1307 cm^{-1}; HRMS (EI): calcd for $C_{22}H_{20}N_2O_2$ [M]$^+$: 344.1525, found 344.1526.

4.2.13. Compound **4m**

Reaction was carried out according to the typical procedure with 1,2-phenylenediamine (**1**, 53 mg, 0.492 mmol), methyl acetoacetate (**2a**, 69 μl, 0.639 mmol), 3-furancarboxaldehyde (**3m**, 43 μl, 0.497 mmol), and $C_6F_5CO_2H$ (20.8 mg, 0.098 mmol) in DCE (4.9 ml) to give **4m** (46.6 mg, 33%). Reaction time for reflux was 3 h. Hexane/AcOEt=3.5:1 was used as eluent for SiO_2 column chromatography. Pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ=10.18 (br s, 1H), 7.40 (d, J=13.8 Hz, 2H), 6.99–6.94 (m, 3H), 6.77–6.74 (m, 1H), 6.37 (s, 1H), 4.85 (t, J=6.3 Hz, 1H), 4.66 (s, 1H), 3.68 (s, 3H), 3.56 (br s, 1H), 2.58 ppm (d, J=6.3 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=170.5, 158.5, 143.5, 138.7, 137.5, 130.8, 128.8, 125.0, 122.34, 122.31, 121.3, 108.3, 84.0, 56.9, 50.4, 38.9 ppm; IR (KBr): 3280, 2358, 2341, 1652, 1616, 1589, 1498, 1299, 1267, 1165 cm^{-1}; HRMS (EI): calcd for $C_{16}H_{16}N_2O_3$ [M]$^+$: 284.1161, found 284.1157.

4.2.14. Compound **4n**

Reaction was carried out according to the typical procedure with 1,2-phenylenediamine (**1**, 53 mg, 0.492 mmol), methyl acetoacetate (**2a**, 69 μl, 0.639 mmol), 2-thiophenecarboxaldehyde (**3n**, 46 μl, 0.492 mmol), and $C_6F_5CO_2H$ (20.8 mg, 0.098 mmol) in DCE (4.9 ml) to give **4n** (80.9 mg, 55%). Reaction time for reflux was 2.5 h. Hexane/AcOEt=9:1 was used as eluent for SiO_2 column chromatography. Pale yellow amorphous; ^{1}H NMR (300 MHz, $CDCl_3$): δ=10.09 (br s, 1H), 7.17–7.13 (m, 1H), 6.94–6.87 (m, 5H), 6.70 (dd, J=5.4, 2.1 Hz, 1H), 5.10 (t, J=6.9 Hz, 1H), 4.58 (s, 1H), 3.65 (br s, 1H), 3.60 (s, 3H), 2.59 ppm (d, J=6.9 Hz, 2H); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ=170.3, 157.8, 148.0, 136.8, 130.9, 126.5, 124.9, 124.4, 123.3, 122.5, 122.2, 121.7, 84.2, 61.0, 50.4, 40.5 ppm; IR (KBr): 3344, 3279, 2947, 2851, 1651, 1614, 1589, 1470, 1435, 1293, 1269, 1232, 1163 cm^{-1}; HRMS (EI): calcd for $C_{16}H_{16}N_2O_2S$ [M]$^+$: 300.0932, found 300.0937.

4.2.15. Compound **4o**

Reaction was carried out according to the typical procedure with 1,2-phenylenediamine (**1**, 53 mg, 0.492 mmol), benzyl acetoacetate

(**2b**, 110 μl, 0.639 mmol), benzaldehyde (**3a**, 50 μl, 0.492 mmol), and $C_6F_5CO_2H$ (20.8 mg, 0.098 mmol) in DCE (4.9 ml) to give **4o** (122.6 mg, 67%). Reaction time for reflux was 2 h. Hexane/AcOEt=6:1 was used as eluent for SiO_2 column chromatography. Pale yellow oil; ^1H NMR (300 MHz, $CDCl_3$): δ=10.23 (br s, 1H), 7.39–7.26 (m, 10H), 7.00–6.87 (m, 3H), 6.76–6.73 (m, 1H), 5.16 (A in ABq, J=12.6 Hz, 1H), 5.12 (B in ABq, J=12.6 Hz, 1H), 4.83 (dd, J=9.0, 4.2 Hz, 1H), 4.67 (s, 1H), 3.69 (br s, 1H), 2.67 (dd, J=13.8, 9.0 Hz, 1H), 2.53 ppm (dd, J=13.8, 4.2 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=169.9, 159.0, 144.7, 137.9, 137.0, 129.7, 128.7, 128.4, 127.9, 127.8, 127.76, 126.0, 125.1, 122.5, 121.5, 120.8, 83.8, 65.2, 64.7 40.2 ppm; IR (KBr): 3280, 3030, 2250, 1666, 1633, 1504, 1234, 1167 cm^{-1}; HRMS (EI): calcd for $C_{24}H_{22}N_2O_2$ $[M]^+$: 370.1681, found 370.1683.

*4.2.16. Compound **4p***

Reaction was carried out according to the typical procedure with 1,2-phenylenediamine (**1**, 53 mg, 0.492 mmol), *tert*-butyl acetoacetate (**2c**, 106 μl, 0.639 mmol), benzaldehyde (**3a**, 50 μl, 0.492 mmol), and $C_6F_5CO_2H$ (20.8 mg, 0.098 mmol) in DCE (4.9 ml) to give **4p** (120.4 mg, 73%). Reaction time for reflux was 1 h. Hexane/AcOEt=6:1 was used as eluent for SiO_2 column chromatography. Pale yellow oil; ^1H NMR (300 MHz, $CDCl_3$): δ=10.20 (br s, 1H), 7.34–7.28 (m, 5H), 6.99–6.76 (m, 3H), 6.74 (d, J=6.0 Hz, 1H), 4.81 (dd, J=9.9, 3.9 Hz, 1H), 4.58 (s, 1H), 3.66 (br s, 1H), 2.68 (dd, J=13.8, 9.9 Hz, 1H), 2.45 (ddd, J=9.9, 3.9, 0.9 Hz, 1H), 1.50 ppm (s, 9H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=170.2, 157.8, 145.1, 137.7, 130.1, 128.8, 127.9, 126.0, 124.7, 122.5, 121.5, 120.8, 85.7, 78.6, 65.2, 40.2, 28.5 ppm; IR (KBr): 3275, 2253, 1793, 1652, 1622, 1589, 1477, 1221, 1153 cm^{-1}; HRMS (EI): calcd for $C_{21}H_{24}N_2O_2$ $[M]^+$: 336.1838, found 336.1828.

*4.2.17. Compound **4q***

$C_6F_5CO_2H$ (20.8 mg 0.098 mmol) was added to the solution of 1,2-phenylenediamine (**1**, 53 mg, 0.492 mmol) and methyl propionylacetate (**2e**, 80 μl, 0.637 mmol) in DCE (4.9 ml) at rt under N_2. The reaction mixture was stirred for 1 h at rt and stirred for 3 h at 50 °C. After the reaction mixture was cooled to rt, benzaldehyde (**3a**, 50 μl, 0.492 mmol) was added to the solution and the reaction mixture was heated at reflux for 2.5 h. After the reaction mixture was cooled to rt, solvent was evaporated in vacuo. The residue was purified by SiO_2 column chromatography (hexane/AcOEt=4.5:1) to afford compound **4q**. Pale yellow oil; ^1H NMR (270 MHz, $CDCl_3$): δ=10.42 (br s, 1H), 7.38–7.20 (m, 5H), 7.05–6.97 (m, 3H), 6.69–6.66 (m, 1H), 4.81 (s, 1H), 4.41 (d, J=9.7 Hz, 1H), 3.72 (s, 3H), 3.63 (br s, 1H), 2.95–2.89 (m, 1H), 0.90 ppm (d, J=9.5 Hz, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ=170.7, 163.7, 143.8, 137.5, 130.5, 128.6, 127.7, 126.1, 124.8, 122.3, 122.0, 121.3 81.1, 72.7, 50.3, 39.5, 15.9 ppm; IR (KBr): 3344, 3271, 2980, 1651, 1612, 1277, 1169 cm^{-1}; HRMS (EI): calcd for $C_{19}H_{20}N_2O_2$ $[M]^+$: 308.1525, found 308.1521.

*4.2.18. Compound **4r***

$C_6F_5CO_2H$ (20.8 mg 0.098 mmol) was added to the solution of 1,2-phenylenediamine (**1**, 53 mg, 0.492 mmol) and methyl 2-oxocyclopentanecarboxylate (**2f**, 79 μl, 0.639 mmol) in DCE (4.9 ml) at rt under N_2. The reaction mixture was stirred for 1 h at rt and stirred for 3 h at 50 °C. After the reaction mixture was cooled to rt, benzaldehyde (**3a**, 50 μl, 0.492 mmol) was added to the solution and the reaction mixture was heated at reflux for 2.5 h. After the reaction mixture was cooled to rt, solvent was evaporated in vacuo. The residue was purified by SiO_2 column chromatography (CH_2Cl_2/AcOEt=50:1) to afford compound **4r**. Colorless solid; mp 159–160 °C; ^1H NMR (300 MHz, CD_2Cl_2): δ=9.86 (br s, 1H), 7.40–7.32 (m, 5H), 6.92–6.68 (m, 3H), 6.65–6.62 (m, 1H), 4.27 (d, J=9.9 Hz, 1H), 3.89 (br s, 1H), 3.71–3.70 (m, 3H), 3.28 (m, 1H), 2.55–2.40 (m, 2H), 1.58–1.34 ppm (m, 2H); ^{13}C NMR (75.5 MHz, CD_2Cl_2): δ=168.1, 160.0, 142.9, 136.4, 128.9, 128.4, 127.6, 127.0, 123.0, 120.6, 120.3, 120.1, 95.0, 64.8, 51.1, 50.0, 26.7, 26.0 ppm; IR (KBr): 3340, 2947, 1734, 1655, 1624, 1589, 1261 cm^{-1}; HRMS (EI): calcd for $C_{20}H_{20}N_2O_2$ $[M]^+$: 320.1525, found 320.1527. Anal. Calcd for $C_{20}H_{20}N_2O_2$: C, 74.98; H, 6.29; N, 8.74. Found C, 74.96; H, 6.38; N, 8.75.

4.3. Studies about γ-selectivity

*4.3.1. Preparation of 3-[(2-aminophenyl)amino]-2-butemoic acid methyl ester (**5**)*

The solution of 1,2-phenylenediamine (**1**, 1.03 g, 9.55 mmol), methyl acetoacetate (**2a**, 1.11 g, 9.55 mmol), and AcOH (0.1 ml, 1.7 mmol) in toluene (30 ml) was heated at reflux for 1 h under N_2. Solvent was evaporated in vacuo and residue was purified by SiO_2 column chromatography (Hexane/AcOEt=7:3) to give **5** (1.09 g) with minor impurity. It was washed with hexane to afford pure **5** (986 mg, 4.78 mmol, 50%) as colorless solid; mp 84 °C; ^1H NMR (270 MHz, $CDCl_3$): δ=9.86 (br s, 1H), 7.08 (ddd, J=7.0, 7.0, 1.4 Hz, 1H), 6.98 (d, J=7.0 Hz, 1H), 6.76–6.68 (m, 2H), 4.73 (s, 1H), 3.83 (br s, 2H), 3.66 (s, 3H), 1.81 ppm (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=170.8, 161.5, 143.4, 128.5, 127.9, 124.6, 118.2, 115.5, 84.6, 50.3, 19.8 ppm; IR (KBr): 3456, 3363, 2365, 1654, 1604, 1267, 1165 cm^{-1}. Anal. Calcd for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84; N, 13.58. Found C, 64.17; H, 6.85; N, 13.51.

*4.3.2. Compound **6***

$C_6F_5CO_2H$ (15.7 mg, 0.074 mmol) was added to the solution of compound **5** (76.3 mg, 0.370 mmol) and 4-chlorobenzaldehyde (**3c**, 54.6 mg, 0.370 mmol) in EtOH (3.7 ml) at rt under N_2 and the reaction mixture was stirred for 1 h. After the completion of the reaction (judged from TLC analysis), the solvent was evaporated in vacuo and residue was purified by SiO_2 column chromatography (hexane/AcOEt=5:3) to afford compound **6** (94.7 mg, 78%). Pale yellow amorphous powder; ^1H NMR (270 MHz, acetone-d_6): δ=7.74 (br s, 1H), 7.23–7.20 (m, 2H), 7.16–7.12 (m, 2H), 6.83–6.80 (m, 1H), 6.59–6.51 (m, 3H), 5.80 (d, J=6.3 Hz, 1H), 5.71 (d, J=6.3 Hz, 1H), 3.52 (s, 3H), 2.53 ppm (s, 3H); ^{13}C NMR (75.5 MHz, acetone-d_6): δ=169.1, 153.0, 144.8, 139.0, 133.3, 132.2, 130.4, 128.8, 123.4, 121.5, 121.3, 120.5, 101.6, 60.7, 51.1, 24.3 ppm; IR (KBr): 3338, 2360, 1676, 1624, 1533, 1274, 1238 cm^{-1}; HRMS (EI): calcd for $C_{18}H_{17}N_2O_2Cl$ $[M]^+$: 328.0978, found 328.0975.

Acknowledgements

This work was financially supported by Grant-in-Aid for Scientific Research (A) and Grant-in-Aid for Scientific Research for Exploratory Research from Japan Society for the Promotion of Science and by Grant-in-Aid for Scientific Research on Priority Areas (17035047) from the Ministry of Education, Culture, Sports, Science, and Technology, Japan. K.M. thanks the Japan Society for the Promotion of Science (JSPS) for a Research Fellowship for Young Scientists.

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