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An efficient synthesis of β-amino esters via Zn(OTf)$_2$-catalyzed Mannich-type reaction

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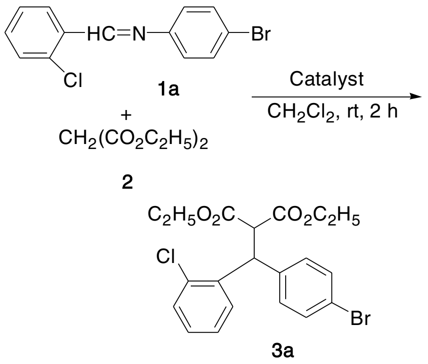
Abstract—A Zn(OTf)$_2$-catalyzed Mannich-type reaction of the electron-deficient aromatic amines with the electron-deficient aromatic aldehydes and diethyl malonic ester was described. This three-component reaction afforded the corresponding β-amino esters in good yields.

β-Amino acids are important structure units of several biologically active compounds, such as dolastins, astins, onchidin, jasplakinolide, and motuporin,[1] and useful building blocks for β-lactams[2] and β-peptides[3] that are present in a variety of drugs.[4] Hence, there is high interest in developing convenient methods for the synthesis of β-amino esters. The Mannich-type reactions are classic methods for the preparation of β-amino carbonyl compounds, including β-amino esters, and very important carbon–carbon bond-forming reactions in organic synthesis.[5] These type of reactions have been extensively used as a key step in the synthesis of various natural products as well as in medicinal chemistry.[6] It has been reported that Lewis acids are able to promote the Mannich-type reactions for the synthesis of β-amino esters.[5a,h,j,7] However, these methods suffer from some disadvantages such as requiring a large amount of Lewis acid (usually more than 10 mol %), a long reaction time, or/and atmosphere sensitive reagents. Herein, we report a Zn(OTf)$_2$-promoted three-component Mannich-type reaction of amine, aldehyde, and diethyl malonic ester, which led to a rapid and efficient synthesis of β-amino esters under mild conditions.

Our initial experiments were carried out using imine **1a** and diethyl malonic ester (**2**) in CH_2Cl_2 at room temperature (Scheme 1). Several Lewis acids Yb(OTf)$_3$, Zn(OTf)$_2$, and $ZnCl_2$ were investigated.[8] It was observed that both Yb(OTf)$_3$ and Zn(OTf)$_2$ were more active than $ZnCl_2$. Using 1 mol % Zn(OTf)$_2$ could give β-amino ester **3a** in satisfactory yield (95%).



Catalyst = Yb(OTf)$_3$ (5 mol %), yield 99%
Yb(OTf)$_3$ (1 mol %), yield 90%
Zn(OTf)$_2$ (1 mol %), yield 95%
$ZnCl_2$ (1 mol %), yield 40%
Catalyst-free, no reaction

Scheme 1.

We then examined a variety of imines using the optimized conditions (Scheme 2, Table 1). It was found that the imines containing electron-withdrawing groups gave good to excellent yields (87–98%) (Table 1, entries 1–6, 10–12, and 16), while the imines containing strong electron-donating groups gave poor yields due to their electron-rich carbon–nitrogen double bonds (Table 1, entries 13–15).

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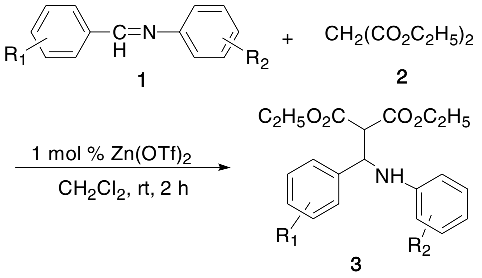


Scheme 2.

Table 1. Reaction of imines with diethyl malonic ester using $Zn(OTf)_2$

Entry	R_1	R_2	Product	Yield[a] (%)
1	*o*-Cl	*p*-Br	**3a**	95
2	*p*-Br	*p*-Cl	**3b**	93
3	*p*-Br	*p*-Br	**3c**	96
4	2,6-Dichloro	*p*-Cl	**3d**	98
5	2,6-Dichloro	*o*-Cl	**3e**	97
6	2,6-Dichloro	*m*-Cl	**3f**	94
7	2,6-Dichloro	*o*-CH_3	**3g**	50
8	*p*-Br	*o*-CH_3	**3h**	40
9	*p*-CH_3	*m*-Cl	**3i**	81
10	*m*-NO_2	*m*-Cl	**3j**	87
11	*o*-Cl	*o*-Cl	**3k**	90
12	*o*-Cl	*m*-Cl	**3l**	89
13	*p*-CH_3O	*p*-Cl	**3m**	20
14	3,4-(OCH_2O)–	*p*-Cl	**3n**	5
15	*p*-CH_3	*p*-CH_3O	**3o**	10
16	H	H	**3w**	50

[a] Isolated yield.

The structure of the β-amino esters **3** is unambiguously supported by an X-ray crystal structure analysis for **3c** (Fig. 1).[9]

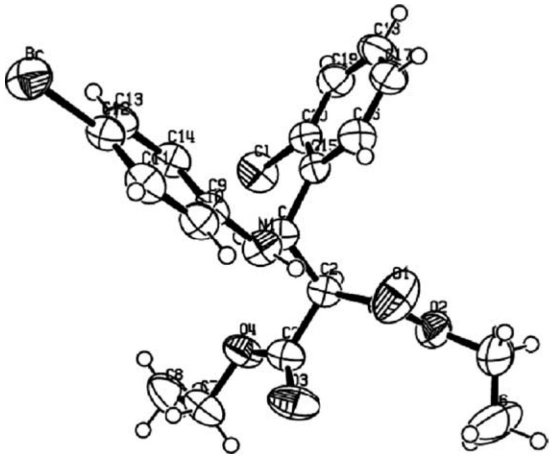
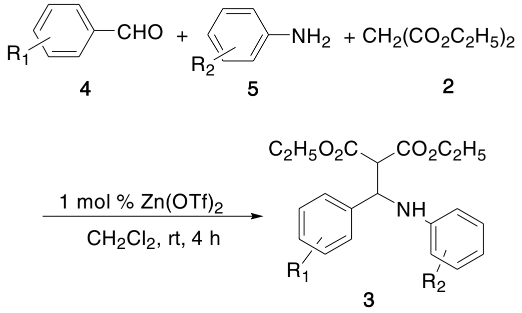


Figure 1. X-ray structure of compound **3a**.



Scheme 3.

Table 2. Three-component reaction of aromatic amines, aromatic aldehyde, and diethyl malonate

Entry	R_1	R_2	Product	Yield[a] (%)
1	*o*-Cl	*p*-Br	**3a**	92
2	*p*-Br	*p*-F	**3p**	90
3	*p*-F	*p*-Cl	**3q**	91
4	2,6-Dichloro	*p*-Br	**3s**	95
5	3,4-Dimethyl	*p*-Br	**3t**	60
6	*m*-NO_2	*m*-Cl	**3j**	96
7	*o*-Cl	*m*-Cl	**3l**	88
8	2,6-Dichloro	*p*-CH_3O	**3r**	45
9	2,6-Dichloro	*o*-CH_3O	**3g**	42
10	3,4-(OCH_2O)–	*p*-Br	**3u**	6
11	*p*-CH_3O	*p*-CH_3O	**3v**	0

[a] Isolated yield.

In connection with our research program aimed at synthesizing important functional structures by multicomponent reactions (MCRs),[10] we investigated the possibility for improving this reaction by an one-pot three-component tandem process in which imines **1** were generated in situ from amines **4** and aldehydes **5** (Scheme 3).[11] As shown in Table 2, the three-component reaction of diethyl malonic ester with the electron-deficient amines and the electron-deficient aldehydes afforded the corresponding β-amino esters **3** in good to excellent yields (85–95%) (Table 2, entries 1–7). However, the electron-rich amines or/and aldehydes gave poor yields (Table 2, entries 8–10) or even no desired product (Table 2, entry 11).

In summary, we have developed a versatile method to synthesize β-amino esters via a $Zn(OTf)_2$-catalyzed Mannich-type reaction of diethyl malonate with imines that can be in situ generated from the corresponding aromatic amines and aromatic aldehydes. The protocol is facile and efficient for the electron-deficient imines or aromatic amines and aromatic aldehydes.

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References and notes

1. Cardillo, G.; Tomasini, C. *Chem. Soc. Rev.* **1996**, 117–128.
2. (a) van der Steen, F. H.; van Koten, G. *Tetrahedron* **1991**, *47*, 7503–7524; (b) Hart, D. J.; Ha, D.-C. *Chem. Rev.* **1989**, *89*, 1447–1465.

3. Krauthäuser, S.; Christianson, L. A.; Powell, D. R.; Gellman, S. H. *J. Am. Chem. Soc.* **1997**, *119*, 11719–11720.
4. Rosenblum, S. B.; Huynh, T.; Afonso, A.; Davis, H. R., Jr.; Yumibe, N.; Clader, J. W.; Burnett, D. A. *J. Med. Chem.* **1998**, *41*, 973–980.
5. (a) Kobayashi, S.; Matsubara, R.; Kitagawa, H. *Org. Lett.* **2002**, *4*, 143–145; (b) Davis, F. A.; Zhang, Y.; Anilkumar, G. *J. Org. Chem.* **2003**, *68*, 8061–8064; (c) Evans, G. B.; Furneaux, R. H.; Tyler, P. C.; Schramm, V. L. *Org. Lett.* **2003**, *5*, 3639–3640; (d) Martin, S. F. *Acc. Chem. Res.* **2002**, *35*, 895–904; (e) Fujita, T.; Nagasawa, H.; Uto, Y.; Hashimoto, T.; Asakawa, Y.; Hori, H. *Org. Lett.* **2004**, *6*, 827–830; (f) Joshi, N. S.; Whitaker, L. R.; Francis, M. B. *J. Am. Chem. Soc.* **2004**, *126*, 15942–15943; (g) Wenzel, A. G.; Jacobern, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 12964–12965; (h) Ueno, M.; Ishitani, H.; Kobayashi, S. *Org. Lett.* **2002**, *4*, 3395–3397; (i) Ishimaru, K.; Kojima, T. *Tetrahedron Lett.* **2003**, *44*, 5441–5444; (j) Badorrey, R.; Cativiela, C.; Diaz-de-Villegas, M. D.; Gálvez, J. A. *Tetrahedron Lett.* **2003**, *44*, 9189–9192; (k) Córdova, A. *Acc. Chem. Res.* **2004**, *37*, 102–112; (l) Wayne, E. J.; Cohen, J. B. *J. Chem. Soc.* **1925**, *127*, 458.
6. For excellent reviews, see: (a) Arend, M.; Westerman, B.; Risch, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 1044–1070; (b) Kabayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069–1094.
7. (a) Periasamy, M.; Suresh, S.; Ganesan, S. S. *Tetrahedron Lett.* **2005**, *46*, 5521–5524; (b) Jacobsen, M. F.; Ionita, L.; Skrydstrup, T. *J. Org. Chem.* **2004**, *69*, 4792–4796; (c) Komoto, I.; Kobayashi, S. *J. Org. Chem.* **2004**, *69*, 680–688; (d) Chung, W. J.; Omote, M.; Welch, J. T. *J. Org. Chem.* **2005**, *70*, 7784–7787; (e) Pandey, G.; Singh, R. P.; Garg, A.; Singh, V. K. *Tetrahedron Lett.* **2005**, *46*, 2137–2140.
8. Typical procedure for the synthesis of **3a**: To a mixture of imine **1a** (4 mmol) and diethyl malonic ester (4 mmol) in CH_2Cl_2 (15 ml) was added $Zn(OTf)_2$ (0.04 mmol). The mixture was stirred at room temperature for 2 h. After completion of the reaction, the solvent was evaporated in vacuum. The resulting residue was purified by a flash column chromatography on silica gel with ethyl acetate–hexane (1:10) as eluent to give pure **3a** as a colorless solid. Mp 106–107 °C; IR (KBr) 3394, 2981, 1745, 1569, 1499, 1375, 1250, 1178 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.38–7.32 (m, 2H), 7.21–7.15 (m, 4H), 6.41 (d, $J = 8.8$ Hz, 2H), 5.80 (d, $J = 9.4$ Hz, 1H), 5.50 (dd, $J = 4.3$, 9.4 Hz, 1H), 4.24–4.02 (m, 5H), 1.20 (t, $J = 7.1$ Hz, 3H), 1.11 (t, $J = 7.1$ Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.5, 167.4, 145.4, 13.16, 133.1, 132.2, 132.1, 130.1, 129.4, 128.8, 127.4, 115.3, 115.2, 109.9, 62.3, 61.8, 54.6, 54.3, 14.2, 14.1 ppm; MS (ESI) *m*/*z* 478 ($[M+Na]^+$). $C_{20}H_{21}BrClNO_4$ (454.74) Calcd: C, 52.82; H, 4.65; N, 3.08. Found: C, 52.78; H, 4.67; N, 2.84.
9. The single crystal of **3a** was successfully grown as a racemic mixture from hexane. CCDC 288449 contains the supplementary crystallographic data for compound **3a**. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.
10. (a) Cui, S. L.; Lin, X. F.; Wang, Y. G. *J. Org. Chem.* **2005**, *70*, 2866; (b) Wang, Y. G.; Lin, X. F.; Cui, S. L. *Synlett* **2004**, 1175; (c) Xia, M.; Wang, Y. G. *Tetrahedron Lett.* **2002**, *43*, 7703.
11. Typical procedure for the synthesis of **3j**: A mixture of 2-chlorophenylamine (4 mmol), 2-nitrobenzaldehyde (4 mmol), diethyl malonic ester (4 mmol), and $Zn(OTf)_2$ (0.04 mmol) in CH_2Cl_2 (15 ml) was stirred at room temperature for 4 h. After removing the solvent in vacuum, the residues were purified by a flash column chromatography on silica gel with ethyl acetate–hexane (1:10) as eluent to afford pure **3j** as a yellow solid. Mp 99–100 °C; IR (KBr) 3398, 1721, 1598, 1531, 1352, 1269 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 8.26 (s, 1H), 8.13–8.11 (m, 1H), 7.73 (t, $J = 7.8$ Hz, 1H), 7.50 (t, $J = 8.0$ Hz, 1H), 6.66–6.64 (m, 1H), 6.57–6.56 (m, 1H), 6.47–6.46 (m, 1H), 6.44 (d, $J = 6.4$ Hz, 1H), 5.56 (d, $J = 9.0$ Hz, 1H), 5.28 (dd, $J = 5.4$, 9.0 Hz, 1H), 4.19–4.08 (m, 4H), 3.91 (d, $J = 5.4$ Hz, 1H), 1.19 (t, $J = 7.1$ Hz, 3H), 1.11 (t, $J = 7.1$ Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.8, 166.8, 148.8, 147.3, 142.1, 135.3, 133.3, 130.5, 130.0, 123.2, 122.1, 118.7, 113.7, 122.1, 62.5, 62.2, 57.7, 56.5, 14.1, 14.0 ppm; MS (ESI) *m*/*z* 444 ($[M+Na]^+$). $C_{20}H_{21}ClN_2O_6$ (420.84) Calcd: C, 57.08; H, 5.03; N, 6.66. Found: C, 57.08; H, 4.90; N 6.58.