

New Three-Component Reaction: Novel Formation of a Seven-Membered Ring by the Unexpected Reaction at the γ -Position of the β -Keto Ester

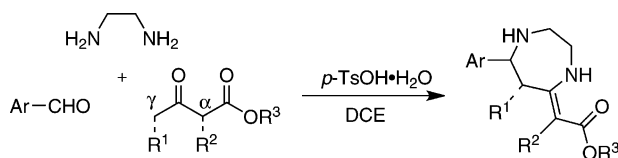
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ABSTRACT



The novel three-component reaction of aromatic aldehydes, ethylenediamine, and β -keto esters is described. In this reaction, β -keto esters react at the γ -position which is generally unreactive to produce the seven-membered ring compounds. Products have secondary amines and β -enamino esters, which can serve in further functionalizations to produce molecular diversity.

Recently, the studies regarding multicomponent reactions (MCRs) have been receiving much attention¹ because of their efficiency and diversity of products. They are very useful in the drug discovery process² and are powerful tools for the total synthesis of complex natural products.³ Many studies for the improvement and application of already known classical MCRs, such as the Mannich reaction,⁴ Ugi reaction,⁵ and Biginelli reaction,⁶ have been reported. However, the

development of a new MCR is still an important issue in the fields of medicinal and organic chemistries.

We now report a novel MCR using aromatic aldehydes, ethylenediamine, and β -keto esters. This reaction is very unique because the C–C bond formation unexpectedly occurs at the generally unreactive γ -position of the β -keto esters, and seven-membered ring products, which are normally difficult to form, are obtained.

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(1) For recent reviews, see: (a) Dömling, A. *Chem. Rev.* **2006**, *106*, 17–89. (b) Banfi, L.; Riva, R. *Org. React.* **2005**, *65*, 1–140. (c) Ramón, D. J.; Yus, M. *Angew. Chem.* **2005**, *117*, 1628–1661; *Angew. Chem., Int. Ed.* **2005**, *44*, 1602–1634. (d) Zhu, J. *Eur. J. Org. Chem.* **2003**, 1133–1144.

(2) (a) Armstrong, R. W.; Combs, A. P.; Tempest, P. A.; Brown, S. D.; Keating, T. A. *Acc. Chem. Res.* **1996**, *29*, 123–131. (b) Schreiber, S. L. *Science* **2000**, *287*, 1964–1969. (c) Werner, S.; Turner, D. M.; Lyon, M. A.; Huryn, D. M.; Wipf, P. *Synlett* **2006**, 2334–2338 and references cited therein.

(3) For examples, see: (a) Endo, A.; Yanagisawa, A.; Abe, M.; Tohma, S.; Kan, T.; Fukuyama, T. *J. Am. Chem. Soc.* **2002**, *124*, 6552–6554. (b) Inanaga, K.; Takasu, K.; Ihara, M. *J. Am. Chem. Soc.* **2004**, *126*, 1352–1353. (c) Powell, D. A.; Batey, R. A. *Org. Lett.* **2002**, *4*, 2913–2916.

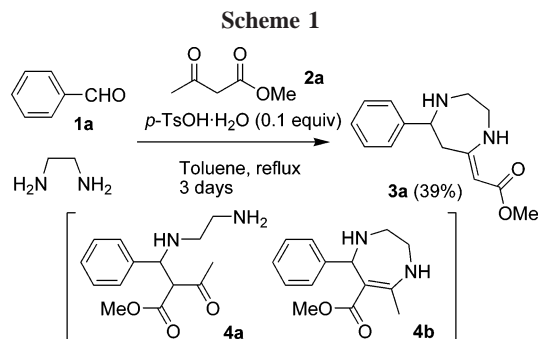
(4) For reviews, see: (a) Marques, M. M. B. *Angew. Chem.* **2006**, *118*, 356–360; *Angew. Chem., Int. Ed.* **2006**, *45*, 348–352. (b) Córdova, A. *Acc. Chem. Res.* **2004**, *37*, 102–112.

(5) For reviews, see: (a) Dömling, A.; Ugi, I. *Angew. Chem.* **2000**, *112*, 3300–3344; *Angew. Chem., Int. Ed.* **2000**, *39*, 3168–3210. For recent studies, see: (b) Giovenzana, G. B.; Tron, G. C.; Paola, S. Di; Menegotto, I. G.; Pirali, T. *Angew. Chem.* **2006**, *118*, 1117–1120; *Angew. Chem., Int. Ed.* **2006**, *45*, 1099–1102. (c) Kaim, L. El; Grimaud, L.; Obler, J. *Angew. Chem.* **2005**, *117*, 8175–8178; *Angew. Chem., Int. Ed.* **2005**, *44*, 7961–7964. (d) Bonnatere, F.; Bois-Choussy, M.; Zhu, J. *Org. Lett.* **2006**, *8*, 4351–4354.

(6) For reviews, see: (a) Kappe, C. O. *Acc. Chem. Res.* **2000**, *33*, 879–888. (b) Kappe, C. O. *QSAR Comb. Sci.* **2003**, *22*, 630–645. For recent research, see: (c) Nilsson, B. L.; Overman, L. E. *J. Org. Chem.* **2006**, *71*, 7706–7714. (d) Cohen, F.; Overman, L. E. *J. Am. Chem. Soc.* **2006**, *128*, 2604–2608. (e) Suzuki, I.; Suzumura, Y.; Takeda, K. *Tetrahedron Lett.* **2006**, *47*, 7861–7864. (f) Debache, A.; Boumoud, B.; Amimour, M.; Belfaitah, A.; Rhouati, S.; Carboni, B. *Tetrahedron Lett.* **2006**, *47*, 5697–5699. (g) Huang, Y.; Yang, F.; Zhu, C. *J. Am. Chem. Soc.* **2005**, *127*, 16386–16387.

Generally, the nucleophilic attacks by the β -keto esters occur at their α -position.⁷ There are many such reactions. For example, known as the Knoevenagel condensation,⁸ the reactions of β -keto esters and aldehydes give the unsaturated keto esters that are α -adducts of the β -keto esters. The most previously reported MCRs using β -keto esters also afford the α -adducts.^{6,9} Only in few cases¹⁰ were γ -adducts obtained in the reaction of aldehydes and β -keto esters, but α -alkylated β -keto esters were used in their cases. No examples of γ -adducts using α -unsubstituted β -keto esters are known in MCRs, to the best of our knowledge. In general, the control of the reaction at the γ -position is difficult, and it is necessary to prepare dianions.¹¹ In our reaction, the γ -adducts are produced without preparing dianions even using α -unsubstituted β -keto esters. Furthermore, the produced seven-membered ring compounds have both secondary amine and enamino ester units, which would serve in further functionalizations to produce molecular diversity. Therefore, they would be expected as new skeletons in drug discovery.

As part of our studies about the synthetic application of the amins prepared from aldehydes and diamines,¹² we realized the unexpected reactivity of the β -keto ester. Thus, the addition of methyl acetoacetate **2a** (1.0 equiv) to a mixture of benzaldehyde **1a** and ethylenediamine (1.0 equiv) under acidic conditions, *p*-TsOH·H₂O (0.1 equiv), produced the seven-membered ring compound **3a**, which was the γ -adduct of **2a**. The C–C double bond of **3a** was determined as *cis* because the signal of NH appears at 8.91 ppm in the ¹H NMR chart for intramolecular hydrogen bonding with the carbonyl group (Scheme 1). We first expected the



formation of the α -adducts **4a** or **4b** from the reactivity of the β -keto esters as described above. This unexpected outcome was very curious. We then studied the reaction in detail.

(7) For a review, see: Benetti, S.; Romagnoli, R.; Risi, C. D.; Spalluto, G.; Zanirato, V. *Chem. Rev.* **1995**, *95*, 1065–1114.

(8) Jones, G. *Org. React.* **1967**, *15*, 204–599.

(9) For a review, see: (a) Simon, C.; Constantieux, T.; Rodriguez, J. *Eur. J. Org. Chem.* **2004**, 4957–4980. For recent studies, see: (b) Liéby-Muller, F.; Constantieux, T.; Rodriguez, J. *J. Am. Chem. Soc.* **2005**, *127*, 17176–17177. (c) Liéby-Muller, F.; Simon, C.; Imhof, K.; Constantieux, T.; Rodriguez, J. *Synlett* **2006**, 1671–1674.

(10) Rodriguez's group reported multicomponent selective α,γ -difunctionalization of cyclic 1,3-dicarbonyl compounds via reversible α -aldol reaction: Habib-Zahmani, H.; Hacini, S.; Charonnet, E.; Rodriguez, J. *Synlett* **2002**, 1827–1830. And related work: Charonnet, E.; Filippini, M.-H.; Rodriguez, J. *Synthesis* **2001**, 788–804.

The reaction conditions were studied using benzaldehyde **1a**, ethylenediamine (1.0 equiv), and methyl acetoacetate **2a** (1.0 equiv). The results are shown in Table 1. For entries

Table 1. Optimization of the Reaction Conditions

entry	solvent	acid	time	yield ^a
1	toluene	<i>p</i> -TsOH·H ₂ O	3 days	39%
2	DCE	—	20 h	59%
3	DCM	—	—	nd ^c
4	DCE	TFA	—	54%
5	—	PPTS	—	48%
6	—	AcOH	—	nd ^c
7	—	CSA	—	56%
8 ^b	—	<i>p</i> -TsOH·H ₂ O	—	59%

^a Isolated yield. ^b All reagents were added successively. ^c nd = not determined on TLC.

1–7, **1a** and ethylenediamine were stirred for 1 h. **2a** and acid were then added to the resulting mixture, and the solution was heated under reflux. For entries 1–3, the effect of the reaction solvent was examined in the presence of *p*-TsOH·H₂O (0.1 equiv). The reaction proceeded in moderate yield in toluene (Table 1, entry 1). When 1,2-dichloroethane (DCE) was used as the solvent, a better result was obtained (Table 1, entry 2). On the other hand, **3a** was not obtained in dichloromethane (DCM) due to the low reaction temperature (Table 1, entry 3). We next studied the acid catalysts, trifluoroacetic acid (TFA), pyridinium *p*-toluenesulfonate (PPTS), AcOH, and camphorsulfonic acid (CSA), in DCE (Table 1, entries 4–7). These acids, except for AcOH, were effective and produced **3a** in moderate yields. The other solvents (THF and CH₃CN) and other acids (TfOH, Tf₂NH, BF₃·Et₂O, and Yb(TfO)₃) were not effective. During the reaction process, the successive addition of **1a**, ethylenediamine, **2a**, and *p*-TsOH·H₂O (0.1 equiv) gave the same good result (Table 1, entry 8). We then determined the conditions in entry 8 of Table 1 as the optimized conditions.

Under the optimized conditions, the reactions of various aldehydes, ethylenediamine, and methyl acetoacetate **2a** in the presence of *p*-TsOH·H₂O (0.1 equiv) were examined (Table 2). Various aromatic aldehydes are available for this reaction (Table 2, entries 1–8).

Although the substitution of the electron-donating methoxy group decreased the yield (Table 2, entry 1), the substitutions

(11) For examples, see: (a) Langer, P.; Bellur, E. *J. Org. Chem.* **2003**, *68*, 9742–9746. (b) Lygo, B. *Tetrahedron* **1995**, *51*, 12859–12868. (c) Jannet, H. B.; Mourabit, A. Al; Gateau-Olesker, A.; Marazano, C.; Mighri, Z. *Tetrahedron: Asymmetry* **1999**, *10*, 2381–2386.

(12) (a) Fujioka, H.; Murai, K.; Ohba, Y.; Hiramatsu, A.; Kita, Y. *Tetrahedron Lett.* **2005**, *46*, 2197–2199. (b) Fujioka, H.; Murai, K.; Ohba, Y.; Hirose, H.; Kita, Y. *Chem. Commun.* **2006**, 832–834. (c) Fujioka, H.; Murai, K.; Kubo, O.; Ohba, Y.; Kita, Y. *Tetrahedron* **2007**, *63*, 638–643.

Table 2. Reactions with Various Aldehydes

entry	aldehyde 1	product 3	yield ^a
1	1b : X= MeO	3b : X= MeO	39%
2	1c : X= Cl	3c : X= Cl	57%
3	1d : X= Br	3d : X= Br	62%
4	1e : X= NO ₂	3e : X= NO ₂	68%
5	1f : X= CN	3f : X= CN	74%
6	1g : X= COOMe	3g : X= COOMe	62%
7			48%
8			48%

^a Isolated yield.

of electron-withdrawing groups such as chloro, bromo, nitro, cyano, and methyl esters resulted in good yields (Table 2, entries 2–6). Heteroaromatic aldehydes such as 2-pyridinecarboxaldehyde **1h** and 2-thiophenecarboxaldehyde **1i** gave moderate yields (Table 2, entries 7 and 8). However, the aliphatic 3-phenyl propionaldehyde did not produce a seven-membered ring compound and gave a complex mixture.

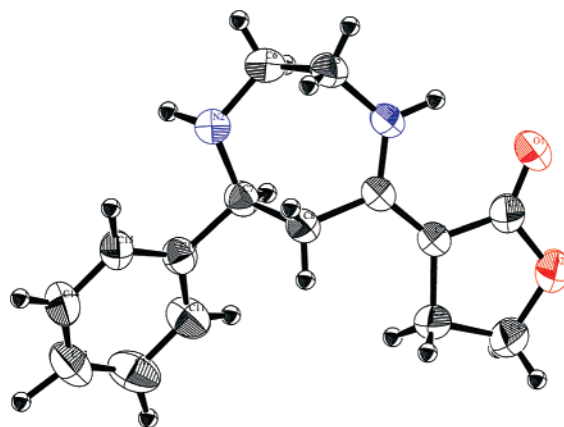
Table 3. Reactions with Various β -Keto Esters

entry	β -keto ester 2	product 3	yield ^a
1			56%
2			27%
3			30%
4			46%
5			69%

^a Isolated yield.

The reactions of various β -keto esters were next studied (Table 3). Benzyl acetoacetate **2b** gave almost the same yield as methyl acetoacetate **2a** (Table 3, entry 1; see entry 8 in Table 1). Substitution of one more methyl group at the γ -position of methyl acetoacetate (methyl 3-oxovalerate **2c**) or one more methyl group at the α -position of methyl acetoacetate (ethyl 2-methylacetoacetate **2d**) decreased the yields (Table 3, entries 2 and 3). On the other hand, interestingly, the cyclic β -keto ester, lactone **2e**, gave the desired enamine ester **3m** in moderate yield (Table 3, entry 4). Furthermore, the cyclic β -keto ester **2f** gave the 5,7-bicyclic compound **3n** in good yield (Table 3, entry 5). Compounds **3k** and **3n** are single diastereomers, and the relationships between the benzyl proton and the homobenzyl proton were determined to be *cis* in both compounds based on their *J* values and NOE studies.¹³

The products of this reaction have the characteristic structures: the enamine ester units of the products were stabilized by hydrogen bonding. Every product in this article shows a proton signal of the NH unit around 8–9.5 ppm in the ¹H NMR chart. The X-ray structure of **3m** also shows that the hydrogen atom of NH is on the same plane as the carbonyl group (Figure 1).

**Figure 1.** X-ray crystal structure of compound **3m**.

To clarify the reaction mechanism, the NMR study was performed as follows. Equimolar amounts of benzaldehyde, ethylenediamine, and methyl acetoacetate were stirred with TFA (0.1 equiv) in CDCl₃ at room temperature and reaction was monitored by ¹H NMR. The ¹H NMR spectrum showed the disappearance of aldehyde and the appearance of imine, and characteristic enamine ester peaks were also observed.¹⁴ This result suggests that at the first stage of the reaction ethylenediamine bridged the aldehyde and the β -keto ester to form imine and enamine ester intermediate **i** (Figure 2). Reflux of the reaction mixture afforded compound **3a**. The

(13) *J* value of benzyl proton: **3k**, *J* = 1.5 Hz; **3n**, *J* = 9.5 Hz. NOEs were observed between the benzyl proton and the homobenzyl proton in both **3k** and **3n**.

(14) For details, see Supporting Information.

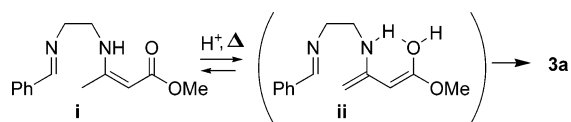
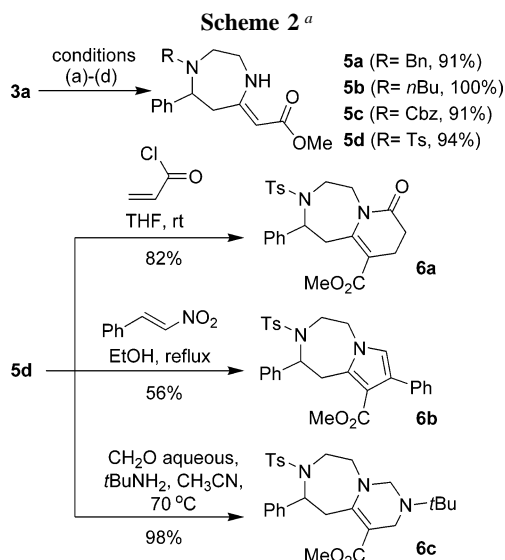


Figure 2. Mechanistic consideration for the formation of **3a**.

γ -selectivity is not clear at this stage. However, we think that the reaction proceeded via such an intermediate **i** and γ -addition occurred maybe through **ii** in an intramolecular fashion for some reason such as hydrogen bonding formation.

The various reactions using the seven-membered ring compound **3a** are shown in Scheme 2. Although compound **3a** has two nitrogen atoms, the secondary amine and the enamino ester amine, the various functional groups such as benzyl, *n*-butyl, benzyloxycarbonyl, and *p*-toluenesulfonyl



^a Conditions: (a) BnBr, K₂CO₃, CH₃CN, 60 °C for **5a**; (b) *n*BuI, K₂CO₃, CH₃CN, reflux for **5b**; (c) CbzCl, K₂CO₃, CH₃CN, H₂O, 0 °C for **5c**; (d) TsCl, Et₃N, DMAP, CH₂Cl₂, 0 °C for **5d**.

functions can be selectively introduced on the nitrogen atom of the secondary amine to give **5a–d**. Many functionalizations of enamino esters have been reported.¹⁵ Their interesting heterocyclic synthesis was applied to **5d** to provide various bicyclic heterocycles. Thus, the reaction with acryloyl chloride gave dihydropyridone **6a**;^{15a} the *trans*- β -nitrostyrene produced the pyrrole **6b**;^{15b} and formaldehyde and *tert*-butylamine gave 1,2,3,4-tetrahydropyrimidine **6c**.^{15c} These results show that the seven-membered ring compounds provide a further functionalization for molecular diversity.

In conclusion, we developed a new three-component coupling reaction of aromatic aldehydes, ethylenediamine, and β -keto esters. This reaction is very interesting as β -keto esters react at the γ -position under usual conditions. Furthermore, the produced seven-membered ring compounds have both secondary amine and enamino esters, which enable further modifications leading to molecular diversity. The potential of the reaction here would then be very high for use in medicinal and synthetic chemistries. Studies on the reaction mechanism and broadening the scopes of the reaction are now in progress.

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Supporting Information Available: Experimental details and detailed spectroscopic data of all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(15) For examples, see: (a) Abelman, M. M.; Curtis, J. K.; James, D. R. *Tetrahedron Lett.* **2003**, *44*, 6527–6531. (b) Baldoli, C.; Cremonesi, G.; Croce, P. D.; Rosa, C. L.; Licandro, E. *Heterocycles* **2004**, *64*, 491–497. (c) Zhao, F. L.; Liu, J. T. *J. Fluorine Chem.* **2004**, *125*, 1841–1845. (d) Bartoli, G.; Cimarelli, C.; Marcantoni, E.; Palmieri, G.; Petrini, M. *J. Org. Chem.* **1994**, *59*, 5328–5335. (e) Cheng, Y.; Yang, H.-B.; Wang, M.-X.; Williams, D. J. *Tetrahedron* **2002**, *58*, 2821–2829.