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Microwave-assisted and $\text{Ln}(\text{OTf})_3$ -catalyzed homo-conjugate addition of *N*-heteroaromatics to activated cyclopropane derivatives

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Abstract

A new expeditious method for the homo-conjugate addition of nitrogen heteroaromatics to 1,1-cyclopropanedicarboxylates was developed in the presence of $\text{La}(\text{OTf})_3$ as an efficient Lewis acid catalyst under microwave irradiation. © 2009 Elsevier Science. All rights reserved

The conjugate addition reactions of amine-nucleophiles including nitrogen heterocycles to α,β -unsaturated carbonyl compounds, so-called aza-Michael reactions, are a convenient way to prepare a pharmacologically important family of β -amino carbonyl compounds.¹ Recently, we found that reactions of this type could be efficiently promoted in water, even in the absence of catalysts, by applying a high-pressure technique.² In our continuing efforts to extend this methodology to other less common Michael acceptors, we have been very interested in the homo-conjugate addition of nitrogen heteroaromatics (*N*-heteroaromatics) to activated cyclopropanes.

Although the ring-opening reaction of activated cyclopropane derivatives with relatively strong nucleophiles is well-established,³ the direct transformation using *N*-heteroaromatics as donor molecules still remains a challenging subject mainly due to their low nucleophilicity.⁴

Our preliminary experiments to realize this strategy using uncatalyzed and high-pressure conditions were all unsuccessful. Gratifyingly, however, we found that microwave irradiation⁵ provided an efficient and expeditious tool for achieving the desired cyclopropane ring-opening reactions with weakly nucleophilic *N*-heteroaromatics in the presence of an appropriate Lewis acid catalyst (Scheme 1).⁶

We describe here the microwave-assisted homo-conjugate addition of a variety of *N*-heteroaromatics **1** to cyclopropanedicarboxylates **2**.

Scheme 1.

To optimize the reaction conditions, we examined the reaction of pyrazole (**1a**, 1.5 equiv) with diethyl 1,1-cyclopropanedicarboxylate (**2a**) in the presence of different Lewis acid catalysts under microwave irradiation. The results are summarized in Table 1.^{7,8}

The results demonstrated that the use of classical Lewis acids such as FeCl_3 and ZnCl_2 did not catalyze the reaction (entries 2, 3, Table 1). On the other hand, in agreement with our previous observations,^{9,10} lanthanide triflates showed remarkable catalytic activities in terms of product yields (entries 4-9, Table 1). Thus, the best result was obtained when the reaction was conducted in the presence of 20 mol% of $\text{La}(\text{OTf})_3$ in MeCN at 120 W and 100 °C for 10 min, and **3a** was produced in 76% yield along with its pyrazolium salt **3b** in 14% yield (entry 5, Table 1).^{11,12} The formation of the latter ionic liquid-type compound can be easily understood by considering the facile quaternization of **3a** with another molecule of **2a**. No reaction occurred in the absence of catalysts (entry 1, Table 1).

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Table 1

Homo-conjugate addition of pyrazole (**1a**) with diethyl 1,1-cyclopropanedicarboxylate (**2a**) under microwave irradiation^a

Entry	cat LA	Yields (%) ^b	
		3a	3b
1 ^c	—	NR ^d	—
2	FeCl ₃	NR ^d	—
3	ZnCl ₂	Trace	—
4	Yb(OTf) ₃	72	19
5	La(OTf) ₃	76	14
6	Nd(OTf) ₃	72	16
7	Gd(OTf) ₃	75	12
8	Dy(OTf) ₃	72	16
9	Sc(OTf) ₃	69	21

^a All reactions were carried out using **1a** (1.5 mmol), **2a** (1.0 mmol) and LA (20 mol%) in MeCN (ca. 2 mL).

^b Isolated yield based on **2a**.

^c Reaction was continued for 30 min.

^d No reaction.

With these results in hand, we then sought to clarify the general scope of this method with various combinations of substrates, and the results are summarized in Table 2.^{7,8}

The reaction of pyrazole (**1a**) with cyclopropanedicarboxylates **2b** and **2c** gave the corresponding adducts **3c** and **3d** in high yields, but the sterically crowded **2d** reacted very slowly to give **3e** in reduced yield (entries 1-3, Table 2). Consistent with the reported examples, the nucleophilic attack of **1a** occurred exclusively at the more-substituted carbon center vicinal to the diester moiety on the cyclopropane ring.¹³ Importantly, in these examples the formation of pyrazolium salts could not be detected probably due to the steric hindrance around the nitrogen atom of a pyrazole ring in the adducts.

Interestingly, the reaction of imidazole (**1b**) and 2-methylimidazole (**1c**) with **2a** or **2b** gave the corresponding adducts **3f**, **3h** and **3j** in good yields along with a considerable amount of their corresponding imidazolium salts **3g**, **3i** and **3k** (entries 4-6, Table 2). When 1,2,4-

triazole (**1d**) was reacted with **2a** and **2b**, the expected regioisomeric products **3l** and **3m** (or **3o** and **3p**) were obtained in good yields in an almost 1 : 1 ratio along with the corresponding triazolium salts **3n** and **3q** (entries 7, 8, Table 2). In a similar manner, benzimidazole (**1e**) and benzotriazole (**1f**) reacted smoothly with **2a** to produce mixtures of **3r** and **3s**, and **3t** and **3u**, respectively, in good combined yields (entries 9, 10, Table 2).

The reaction of purine (**1g**) with **2a** gave a mixture of N9- and N7-substituted regioisomers **3v** and **3w** in respective yields of 41 and 33%, along with a trace amount of N3 (or N1)-substituted **3x** (entry 11, Table 2).¹⁴

To confirm the ease of formation of ionic liquid-type salts during the cyclopropane ring-opening process, stepwise conversion was examined (Scheme 2).¹⁵ Thus, treatment of pre-formed adduct **3a** with 1 equiv of **2a** in the presence of La(OTf)₃ (20 mol%) under the standard conditions (MeCN, 120 W, 10 min, 100 °C, 50 psi) gave **3b** in 22% conversion (15% isolated) yield. This suggests that the in situ-generated zwitterionic intermediate should be protonated spontaneously during the work-up procedure.

Scheme 2.

In conclusion, we have developed a novel method for the homo-conjugate addition of a variety of nitrogen heteroaromatics to activated cyclopropanes in the presence of La(OTf)₃ as an efficient Lewis acid catalyst under microwave irradiation.¹⁶ This method will provide a new rapid method for preparing γ -amino carbonyl compounds, which are known to be important building blocks for natural products and synthetic drugs.¹⁷ Further studies to extend the scope of this new method are now in progress in our laboratory.

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Table 2

Homo-conjugate addition of *N*-heteroaromatics to 1,1-cyclopropanedicarboxylates under microwave irradiation^a

Entry	Substrate	Acceptor	Time (min)	Products (yield, %) ^b	
1	1a	2b	10	3c (83)	
2	1a	2c	10	3d (89)	
3	1a	2d	40	3e (37) ^c	
4	1b	2a	10	3f (40)	3g (36)
5	1b	2b	10	3h (41)	3i (28)
6	1c	2a	10	3j (48)	3k (26)
7	1d	2a	40	3l (37)	3n (21)
				3m (33)	
8	1d	2b	10	3o (37)	3q (19)
				3p (20)	

Table 2

Homo-conjugate addition of *N*-heteroaromatics to 1,1-cyclopropanedicarboxylates under microwave irradiation^a (continued)

Entry	Substrate	Acceptor	Time (min)	Products (yield, %) ^b
9	1e	2a	10	3r (45) 3s (22)
10	1f	2a	10	3t (52) 3u (33)
11	1g	2a	5	3v (41) 3x (trace) or 3w (33)

^a All reactions were carried out using **1** (1.5 mmol), **2** (1.0 mmol) and La(OTf)₃ (20 mol%) in MeCN (ca. 2 mL) at 120 W, 100 °C under 50 psi.^b Isolated yield based on **2**.^c 33% of the recovered **2d** was observed, accompanying by considerable decomposition of substrates.

References and notes

- Reviews: (a) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon: New York 1992; p. 114; (b) Liu, M.; Sibi, M. P. *Tetrahedron* **2002**, *58*, 7991; (c) Vicario, J. L.; Badía, D.; Carrillo, L. *Org. Prep. Proc. Int.* **2005**, *37*, 513; (d) Xu, L.-W.; Xia, C.-G. *Eur. J. Org. Chem.* **2005**, 633.
- Uddin, Md. I.; Nakano, K.; Ichikawa, Y.; Kotsuki, H. *Synlett* **2008**, 1402.
- Reviews: (a) Danishefsky, S. *Acc. Chem. Res.* **1979**, *12*, 66; (b) Wong, H. N. C.; Hon, M.-Y.; Tse, C.-W.; Yip, Y.-C.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165; (c) Reissig, H.-U.; Zimmer, R. *Chem. Rev.* **2003**, *103*, 1151; (d) Yu, M.; Pagenkopf, B. L. *Tetrahedron* **2005**, *61*, 321.
- For related works on base-promoted transformations, see: (a) Franco, F.; Greenhouse, R.; Muchowski, J. M. *J. Org. Chem.* **1982**, *47*, 1682; (b) Ortiz, C.; Greenhouse, R. *Tetrahedron Lett.* **1985**, *26*, 2831; (c) Gibson, C. L.; La Rosa, S.; Ohta, K.; Boyle, P. H.; Leurquin, F.; Lemacon, A.; Suckling, C. J. *Tetrahedron* **2004**, *60*, 943; (d) Kalayanov, G.; Jaksa, S.; Scarcia, T.; Kobe, J. *Synthesis* **2004**, 2026; (e) Torii, T.; Yamashita, K.; Kojima, M.; Suzuki, Y.; Hijiya, T.; Izawa, K. *Nucleosides, Nucleotides & Nucleic Acids* **2006**, *25*, 625; (f) Tanaka, M.; Ubukata, M.; Matsuo, T.; Yasue, K.; Matsumoto, K.; Kajimoto, Y.; Ogo, T.; Inaba, T. *Org. Lett.* **2007**, *9*, 3331.
- The enormous power of microwave irradiation reactions has been well-established in a wide range of organic transformations. See: (a) *Microwave Assisted Organic Synthesis*; Tierney, J. P.; Lidström, P., Eds.; CRC Press: USA and Canada, 2005; (b) *Microwave Methods in Organic Synthesis*; Larhed, M.; Olofsson, K., Eds.; Springer: Berlin, 2006.
- We also examined the reaction of the Na salt of **1a** with **2a** (1.2 equiv) in refluxing DMF for 12 h, but no product formation was observed.
- Microwave irradiation was carried out in a Discovery microwave heating apparatus with a temperature controller. *General procedure*: A mixture of *N*-heteroaromatic **1** (1.5 mmol), cyclopropanedicarboxylate **2** (1.0 mmol) and La(OTf)₃ (0.2 mmol) in MeCN (ca. 2.0 mL) was placed in a microwave reaction vessel, and the mixture was allowed to react at 120 W, 100 °C and 50 psi for a period indicated in Tables 1 and 2. After cooling to rt, the mixture was purified by silica gel column chromatography (elution with CH₂Cl₂-*i*-PrOH) to afford the adduct **3** in some cases together with its salt.
- All new compounds gave satisfactory spectral data.

9. Kotsuki, H.; Arimura, K.; Maruzawa, R.; Ohshima, R. *Synlett* **1999**, 650.
10. For related works on $\text{Ln}(\text{OTf})_3$ -catalyzed cyclopropane ring-opening reactions, see: (a) Kang, Y.-B.; Tang, Y.; Sun, X.-L. *Org. Biomol. Chem.* **2006**, *4*, 299; (b) Karadeolian, A.; Kerr, M. A. *J. Org. Chem.* **2007**, *72*, 10251; (c) Perreault, C.; Goudreau, S. R.; Zimmer, L. E.; Charette, A. B. *Org. Lett.* **2008**, *10*, 689; (d) Carson, C. A.; Young, I. S.; Kerr, M. A. *Synthesis* **2008**, 485; (e) Jackson, S. K.; Karadeolian, A.; Driega, A. B.; Kerr, M. A. *J. Am. Chem. Soc.* **2008**, *130*, 4196 and references cited therein.
11. Compound **3a**: colorless oil; FTIR (neat) ν 1747, 1732, 1515 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 1.26 (6H, t, $J = 7.1$ Hz), 2.45 (2H, q, $J = 7.1$ Hz), 3.28 (1H, t, $J = 7.1$ Hz), 4.19 (2H, q, $J = 7.1$ Hz), 4.20 (2H, q, $J = 7.1$ Hz), 4.23 (2H, t, $J = 7.1$ Hz), 6.24 (1H, dd, $J = 2.2$, 1.9 Hz), 7.38 (1H, d, $J = 2.2$ Hz), 7.51 (1H, d, $J = 1.9$ Hz); ^{13}C NMR (CDCl_3 , 100 MHz) δ 13.9 ($\times 2$), 29.2, 48.8, 49.2, 61.5 ($\times 2$), 105.4, 129.3, 139.6, 168.7 ($\times 2$). Compound **3b**: colorless oil; FTIR (neat) ν 1728, 1283, 1254, 1032 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 1.28 (12H, t, $J = 7.1$ Hz), 2.47 (4H, q, $J = 6.8$ Hz), 3.60 (2H, t, $J = 6.8$ Hz), 4.15-4.27 (8H, m), 4.74 (4H, t, $J = 6.8$ Hz), 6.75 (1H, t, $J = 2.9$ Hz), 8.30 (2H, d, $J = 2.9$ Hz); ^{13}C NMR (CDCl_3 , 100 MHz) δ 13.9 ($\times 4$), 28.1 ($\times 2$), 47.9 ($\times 2$), 48.2 ($\times 2$), 62.2 ($\times 4$), 108.3, 137.8 ($\times 2$), 168.2 ($\times 4$).
12. The reaction of **1a** with the Meldrum's acid derivative **4** in the presence of 20 mol% of $\text{La}(\text{OTf})_3$ under the similar conditions gave **5** in 66% yield accompanying by acylation and decarboxylation:

Compound **5**: mp 52-53 °C; FTIR (KBr) ν 1739, 1420, 1388 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 2.36 (2H, quintet, $J = 6.8$ Hz), 3.15 (2H, t, $J = 6.8$ Hz), 4.28 (2H, t, $J = 6.8$ Hz), 6.24 (1H, t, $J = 2.0$ Hz), 6.44 (1H, dd, $J = 2.7$, 1.4 Hz), 7.41 (1H, d, $J = 2.0$ Hz), 7.50 (1H, d, $J = 2.0$ Hz), 7.69 (1H, d, $J = 1.4$ Hz), 8.24 (1H, d, $J = 2.7$ Hz); ^{13}C NMR (CDCl_3 , 100 MHz) δ 25.0, 30.8, 50.8, 105.4, 109.6, 128.2, 129.2, 139.5, 144.0, 171.2.

13. The higher reactivity at the more-substituted carbon center vicinal to the diester moiety on the cyclopropane ring has been well established. For example, see ref 3a.
14. Assignments of N-9 (**3v**) versus N-7 (**3w**) isomers can be made from the ^{13}C NMR signals of the C-4 and C-5 peaks; for **3v**: δ 134.0 and 151.4; for **3w**: δ 125.1 and 160.8. For comparison, see: (a) Gómez, J. A.; Campos, J.; Marchal, J. A.; Trujillo, M. A.; Melguizo, C.; Prados, J.; Gallo, M. A.; Aránega, A.; Espinosa, A. *Tetrahedron* **1997**, *53*, 7319; (b) Núñez, M. C.; Pavani, M. G.; Díaz-Gavilán, M.; Rodríguez-Serrano, F.; Gómez-Vidal, J. A.; Marchal, J. A.; Aránega, A.; Gallo, M. A.; Espinosa, A.; Campos, J. M. *Tetrahedron* **2006**, *62*, 11724.

Compound **3v**: colorless oil; FTIR (neat) ν 1745, 1731, 1597, 1580 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 1.26 (6H, t, $J = 7.1$ Hz), 2.55 (2H, q, $J = 7.1$ Hz), 3.35 (1H, t, $J = 7.1$ Hz), 4.12-4.24 (4H, m), 4.44 (2H, t, $J = 7.1$ Hz), 8.13 (1H, s), 9.00 (1H, s), 9.16 (1H, s); ^{13}C NMR (CDCl_3 , 100 MHz) δ 14.0 ($\times 2$), 28.7, 41.4, 48.9, 61.9 ($\times 2$), 134.0 (C-4), 145.2, 148.7, 151.4 (C-5), 152.7, 168.3 ($\times 2$).

Compound **3w**: pale yellow oil; FTIR (neat) ν 1742, 1729, 1605, 1561 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 1.27 (6H, t, $J = 7.1$ Hz), 2.51 (2H, q, $J = 7.1$ Hz), 3.34 (1H, t, $J = 7.1$ Hz), 4.15-4.27 (4H, m), 4.44 (2H, t, $J = 7.1$ Hz), 8.23 (1H, s), 9.05 (1H, s), 9.18 (1H, s); ^{13}C NMR (CDCl_3 , 100 MHz) δ 14.0 ($\times 2$), 28.9, 43.6, 48.5, 62.1 ($\times 2$), 125.1 (C-4), 140.0, 147.9, 153.5, 160.8 (C-5), 168.1 ($\times 2$).

15. The use of microwave techniques for the preparation of ionic liquid-type salts has been reported previously. For example, see: Fu, S.-K.; Liu, S.-T. *Synth. Commun.* **2006**, *36*, 2059 and related references cited therein.
16. The reaction using indole itself as an *N*-heteroaromatic under the standardized conditions caused only C-alkylation even in low yield (ca. 6%). For similar findings, see: (a) Harrington, P.; Kerr, M. A. *Tetrahedron Lett.* **1997**, *38*, 5949; (b) Kerr, M. A.; Keddy, R. G. *Tetrahedron Lett.* **1999**, *40*, 5671; (c) England, D. B.; Kuss, T. D. O.; Keddy, R. G.; Kerr, M. A. *J. Org. Chem.* **2001**, *66*, 4704.
17. (a) Vicario, J. L.; Rodríguez, M.; Badía, D.; Carrillo, L.; Reyes, E. *Org. Lett.* **2004**, *6*, 3171; (b) Chi, Y.; Guo, L.; Kopf, N. A.; Gellman, S. H. *J. Am. Chem. Soc.* **2008**, *130*, 5608 and related references cited therein.