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

Md. Imam Uddin, Akiko Mimoto, Keiji Nakano, Yoshiyasu Ichikawa, and Hiyoshizo Kotsuki*
Laboratory of Natural Product Chemistry, Faculty of Science, Kochi University, Akebono-cho, Kochi 780-8520, Japan
Microwave-assisted and Ln(OTf)$_3$-catalyzed homo-conjugate addition of $N$-heteroaromatics to activated cyclopropane derivatives

Md. Imam Uddin, Akiko Mimoto, Keiji Nakano, Yoshiyasu Ichikawa,
and Hiyoshizo Kotsuki*

Laboratory of Natural Product Chemistry, Faculty of Science, Kochi University, Akebono-cho, Kochi 780-8520, Japan

Received Month XX, 2008; Accepted Month XX, 2008 [TL RECEIPT]

Abstract

A new expeditious method for the homo-conjugate addition of nitrogen heteroaromatics to 1,1-cyclopropanedicarboxylates was developed in the presence of La(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 $\alpha,\beta$-unsaturated carbonyl compounds, so-called aza-Michael reactions, are a convenient way to prepare a pharmacologically important family of $\beta$-amino carbonyl compounds. 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. 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 weak nucleophiles is well-established, the direct transformation using $N$-heteroaromatics as donor molecules still remains a challenging subject mainly due to their low nucleophilicity.

Our preliminary experiments to realize this strategy using uncatalyzed and high-pressure conditions were all unsuccessful. Gratifyingly, however, we found that microwave irradiation 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).

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.

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, 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 La(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). 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).
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.

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.

**Acknowledgment**

This work was supported in part by a Scientific Research on Priority Areas (18037053 & 18032055) from MEXT, as well as by a Special Research Grant for Green Science from Kochi University. We also thank the Asahi Glass Foundation for financial support of this work.
<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Acceptor</th>
<th>Time (min)</th>
<th>Products (yield, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>2b</td>
<td>10</td>
<td>3c (83)</td>
</tr>
<tr>
<td>2</td>
<td>1a</td>
<td>2c</td>
<td>10</td>
<td>3d (89)</td>
</tr>
<tr>
<td>3</td>
<td>1a</td>
<td>2d</td>
<td>40</td>
<td>3e (37)</td>
</tr>
<tr>
<td>4</td>
<td>1b</td>
<td>2a</td>
<td>10</td>
<td>3f (40) 3g (36)</td>
</tr>
<tr>
<td>5</td>
<td>1b</td>
<td>2b</td>
<td>10</td>
<td>3h (41) 3i (28)</td>
</tr>
<tr>
<td>6</td>
<td>1c</td>
<td>2a</td>
<td>10</td>
<td>3j (48) 3k (26)</td>
</tr>
<tr>
<td>7</td>
<td>1d</td>
<td>2a</td>
<td>40</td>
<td>3l (37) 3m (33)</td>
</tr>
<tr>
<td>8</td>
<td>1d</td>
<td>2b</td>
<td>10</td>
<td>3o (37) 3p (20) 3q (19)</td>
</tr>
</tbody>
</table>
Homo-conjugate addition of \(N\)-heteroaromatics to 1,1-cyclopropanedicarboxylates under microwave irradiation* (continued)

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

*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.

\(^{33}\)% of the recovered 2d was observed, accompanying by considerable decomposition of substrates.

References and notes


6. 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.

7. 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 \(\text{CH}_2\text{Cl}_2\)-i-PrOH) to afford the adduct 3 in some cases together with its salt.

8. All new compounds gave satisfactory spectral data.
11. Compound 3a: colorless oil; FTIR (neat) v 1747, 1732, 1515 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 1.26 (6H, t, J = 7.1 Hz), 2.45 (2H, q, J = 7.1 Hz), 3.28 (1H, t, J = 1.9 Hz), 7.50 (1H, d, J = 6.8 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); ¹³C NMR (CDCl₃, 100 MHz) δ 13.9 (x2), 29.2, 48.8, 49.2, 61.5 (x2), 105.4, 129.3, 139.6, 168.7 (x2).

Compound 3b: colorless oil; FTIR (neat) v 1728, 1283, 1254, 1032 cm⁻¹; ¹H NMR (CDCl₃, 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); ¹³C NMR (CDCl₃, 100 MHz) δ 13.9 (x4), 28.1 (x2), 47.9 (x2), 48.2 (x2), 62.2 (x4), 108.3, 137.8 (x2), 168.2 (x4).

12. The reaction of 1a with the Meldrum’s acid derivative 4 in the presence of 20 mol% of La(OTf)₃ under the standardized conditions gave 5 in 66% yield accompanying by acylation and decarboxylation.

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 ¹³C 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.; Aráñega, A.; Espinosa, A. Tetrahedron 1997, 53, 7319; (b) Núñez, M. C.; Pavan, M. G.; Díaz-Gavilán, M.; Rodríguez-Serrano, F.; Gómez-Vidal, J. A.; Marchal, J. A.; Aráñega, A.; Gallo, M. A.; Espinosa, A.; Campos, J. M. Tetrahedron 2006, 62, 11724.