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

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ABSTRACT

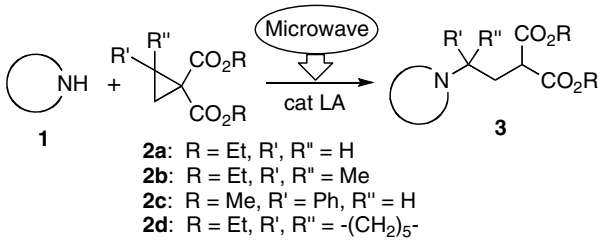
A new expeditious method for the homo-conjugate addition of nitrogen heteroaromatics to 1,1-cyclopropanedicarboxylates was developed in the presence of La(OTf)$_3$ as an efficient Lewis acid catalyst under microwave irradiation.



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.

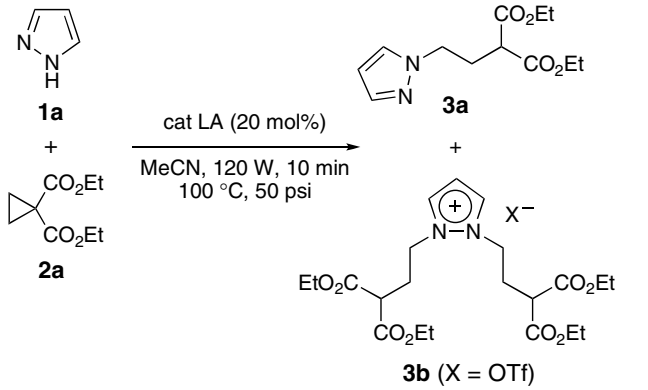
Although the ring-opening reaction of activated cyclopropane derivatives with relatively strong nucleophiles is well-established,[3] the direct transformation using N-heteroaromatics as donor molecules still remains a challenging subject mainly due to their low nucleophilicity.[4]

Our preliminary experiments to realize this strategy using uncatalyzed and high-pressure conditions were all unsuccessful. Gratifyingly, however, we found that microwave irradiation[5] 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]




**Scheme 1.**

**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.

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**Table 2**
Homo-conjugate addition of N-heteroaromatics to 1,1-cyclopropanedicarboxylates under microwave irradiation[a]

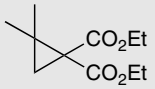
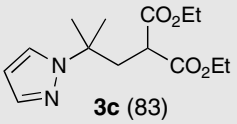
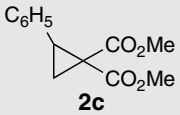
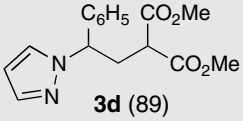
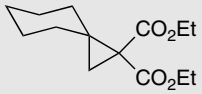
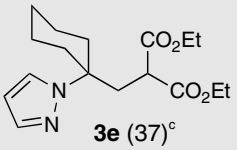
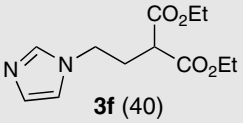
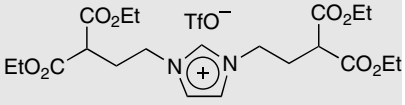
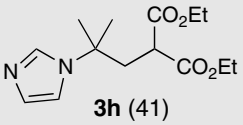
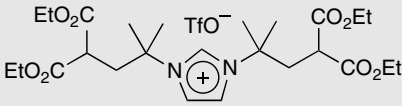
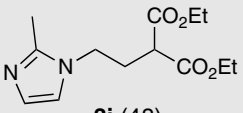
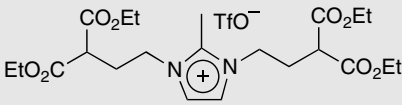
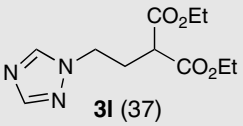
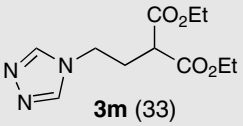
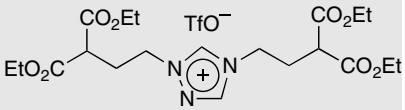
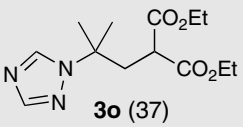
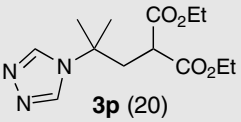
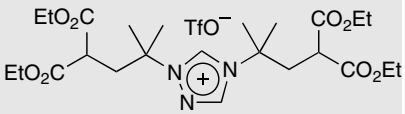
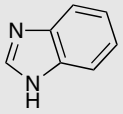
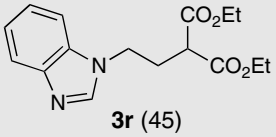
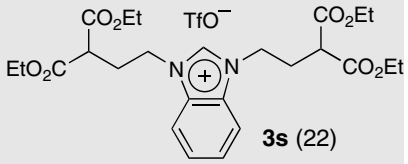
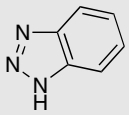
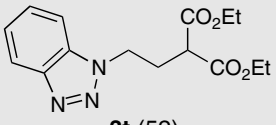
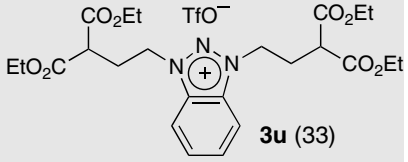
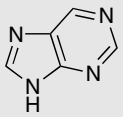
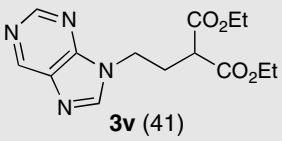
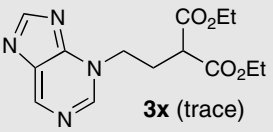
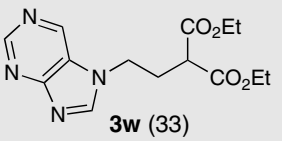
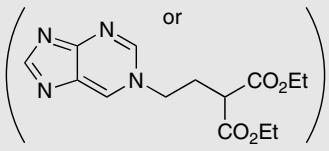
| Entry | Substrate | Acceptor | Time (min) | Products (Yield, %)[b] |
|---|---|---|---|---|
| 1 |  **1a** |  **2b** | 10 |  **3c** (83) |
| 2 | **1a** |  **2c** | 10 |  **3d** (89) |
| 3 | **1a** |  **2d** | 40 |  **3e** (37)[c] |
| 4 |  **1b** | **2a** | 10 |  **3f** (40)  **3g** (36) |
| 5 | **1b**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

**Table 2** (*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, accompanied by considerable decomposition of substrates.

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

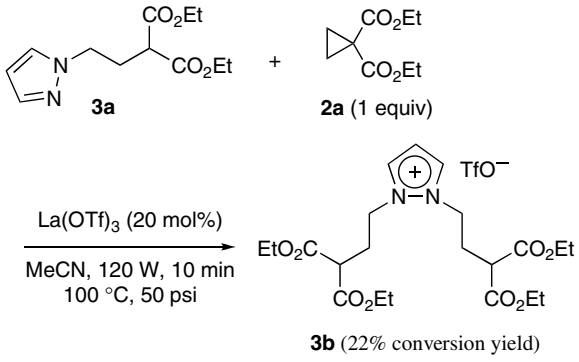
To optimize the reaction conditions, we examined the reaction of pyrazole (**1a**, 1.5 equiv) with diethyl 1,1-cyclopropanedicarboxylate (**2a**) in the presence of different Lewis acid catalysts under microwave irradiation. The results are summarized in Table 1.[7,8]

The results demonstrated that the use of classical Lewis acids such as $FeCl_3$ and $ZnCl_2$ did not catalyze the reaction (entries 2 and 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 (Table 1, entries 4–9). 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 (Table 1, entry 5).[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 (Table 1, entry 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 (Table 2, entries 1–3). 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** (Table 2, entries 4–6). 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** (Table 2, entries 7 and 8). 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 (Table 2, entries 9 and 10).




**Scheme 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** (Table 2, entry 11).[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.

## Acknowledgements

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5. (a) The enormous power of microwave irradiation reactions has been well established in a wide range of organic transformations. See: *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.
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 $CH_2Cl_2$–*i*-PrOH) to afford the adduct **3** in some cases together with its salt.
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11. Compound **3a**: Colorless oil; FTIR (neat) $\nu$ 1747, 1732, 1515 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 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) $\delta$ 13.9 (×2), 29.2, 48.8, 49.2, 61.5 (×2), 105.4, 129.3, 139.6, 168.7 (×2).
    Compound **3b**: Colorless oil; FTIR (neat) $\nu$ 1728, 1283, 1254, 1032 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 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) $\delta$ 13.9 (×4), 28.1 (×2), 47.9 (×2), 48.2 (×2), 62.2 (×4), 108.3, 137.8 (×2), 168.2 (×4).
12. The reaction of **1a** with the Meldrum acid derivative **4** in the presence of 20 mol % of $La(OTf)_3$ under the similar conditions gave **5** in 66% yield accompanied by acylation and decarboxylation


    Compound **5**: mp 52–53 °C; FTIR (KBr) $\nu$ 1739, 1420, 1388 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 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) $\delta$ 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**: $\delta$ 134.0 and 151.4; for **3w**: $\delta$ 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) Núnez, 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) $\nu$ 1745, 1731, 1597, 1580 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 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 (2 H, t, $J$ = 7.1 Hz), 8.13 (1H, s), 9.00 (1H, s), 9.16 (1H, s); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 14.0 (×2), 28.7, 41.4, 48.9, 61.9 (×2), 134.0 (C-4), 145.2, 148.7, 151.4 (C-5), 152.7, 168.3 (×2).
    Compound **3w**: Pale yellow oil; FTIR (neat) $\nu$ 1742, 1729, 1605, 1561 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 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) $\delta$ 14.0 (×2), 28.9, 43.6, 48.5, 62.1 (×2), 125.1 (C-4), 140.0, 147.9, 153.5, 160.8 (C-5), 168.1 (×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.; Rodriguez, 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.