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# Nucleophilic Ring Opening of Cyclopropane Hemimalonates Using Internal Brønsted Acid Activation

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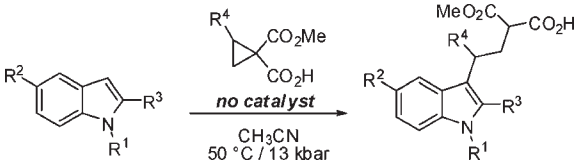
## ABSTRACT




**The reaction of cyclopropanes, geminally disubstituted with one carboalkoxy and one carbohydroxy group, undergoes ring-opening reactions with indole nucleophiles under catalyst-free, hyperbaric (13 kbar) conditions. An internal hydrogen bond is postulated as the mode of activation obviating the need for the Lewis acid catalyst normally used for such donor–acceptor cyclopropane chemistry. These conditions avoid decarboxylation and yield useful adducts with the carboxylic acid group intact for further elaboration.**

Efficient means for the functionalization of indoles remains an active challenge in the field of synthetic organic chemistry.[1] This challenge is fueled by the presence of the indole structure as a scaffold for pharmaceutical drug discovery and its prominence in natural product architecture. A number of years ago, we reported the first example of the nucleophilic ring opening of 1,1-cyclopropane diesters **1** by indoles **2** to yield adducts **4** (Figure 1).[2] Subsequent research found that, when the 3-position was already alkylated, the putative intermediate **3** either underwent pentannulation to **5** or underwent migration to the 2-position to yield products such as **6**.[3,4]

In a research effort directed toward discovering new modes of cyclopropane activation, we were surprised to find that simply saponification of one of the geminal esters produced a hemimalonate **8**, which was a reactive

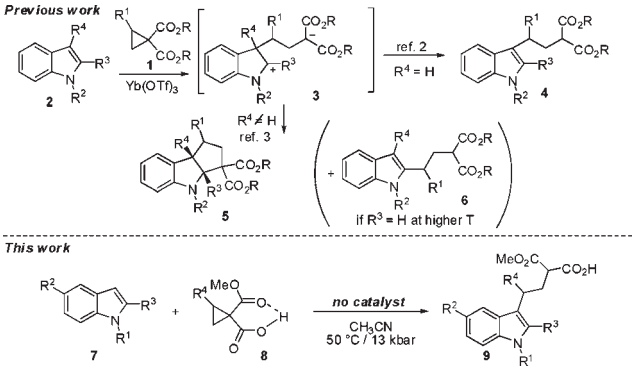



**Figure 1.** Indole functionalization.

electrophile in reactions with indoles **7** in the absence of the lanthanide catalyst, and yielded malonic monoesters **9**. Herein we report the results of this research.[5]

We commenced this project with a short study to determine the optimal reaction conditions (Table 1) for the catalyst-free additions of indoles to cyclopropane-1, 1-hemimalonates. For this work, we chose cyclopropane **8d** for its ease of preparation via monosaponification of the diester (vide infra) as well as its well-behaved performance

(1) For reviews on the synthesis and functionalization of indoles, see: (a) Bandini, M.; Eichholzer, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 9608. (b) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875. (c) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873. (d) Sundberg, R. J. *Indoles*; Academic: New York, 1996.

(2) Harrington, P. E.; Kerr, M. A. *Tetrahedron Lett.* **1997**, *38*, 5949.

(3) (a) England, D. B.; Woo, T. K.; Kerr, M. A. *Can. J. Chem.* **2002**, *80*, 992. (b) England, D. B.; Kuss, T. D. O.; Keddy, R. G.; Kerr, M. A. *J. Org. Chem.* **2001**, *66*, 4704. (c) Kerr, M. A.; Keddy, R. G. *Tetrahedron Lett.* **1999**, *40*, 5671.

(4) Bajtos, B.; Yu, M.; Zhao, H.; Pagenkopf, B. L. *J. Am. Chem. Soc.* **2007**, *129*, 9631.

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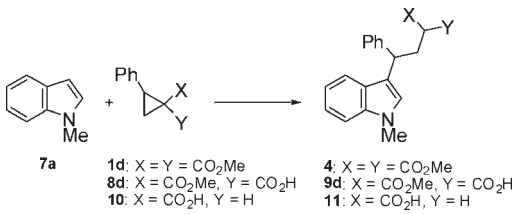
**Table 1.** Optimization Studies




| entry | cyclopropane | temp | indole equiv | conditions | conversion (%) | product (yield) |
|---|---|---|---|---|---|---|
| 1 | **8d** | rt | 2 | 24 h | 0 | N/A |
| 2 | **8d** | 82 °C | 2 | 24 h | 0 | N/A |
| 3 | **8d** | 80 °C | 2 | 30 min, MW | 0 | N/A |
| 4 | **8d** | rt | 2 | 48 h, 13 kbar | 100 | **9d** (70%) |
| 5 | **8d** | rt | 1.2 | 48 h, 13 kbar | 50 | **9d** (not obtained) |
| 6 | **1d** | rt | 2 | 48 h, 13 kbar | 0 | N/A |
| 7 | **10** | rt | 2 | 48 h, 13 kbar | 0 | N/A |
| 8 | **8d** | 50 °C | 2 | 1 h, 13 kbar | 100 | **9d** (76%) |
| 9 | **8d** | 50 °C | 1.2 | 1 h, 13 kbar | 100 | **9d** (73%) |

(as the diester) in our previous work. Several points from Table 1 are worthy of mention, the most notable of which is the fact that the reaction proceeded only under the influence of hyperbaric conditions (entry 4). Ambient, conventionally thermal, and microwave conditions failed to induce a detectable conversion to the ring-opened adduct **4** (entries 1−3). Perhaps this is not so unexpected since the volume of activation for such a ring-opening reaction is expected to be significantly negative. While specific data for cyclopropane ring openings are not documented (to our knowledge), the related ring-opening reactions of epoxides are known to have a significantly negative volume of activation.[6] Moreover, indoles have been shown to effectively add to epoxides under hyperbaric (10 kbar) conditions.[7] An important consequence of the hyperbaric conditions used here is the suppression of the decarboxylation that one might expect under conventional thermal conditions. This allows for use of the carboxylic acid at a later stage.

As a control experiment, we evaluated the reactivity of the parent **1d**, as well as the related cyclopropane **10**, which bore a single carboxylic acid as the only electron-withdrawing group. When entries 4 and 6 were compared, we observed that while hemimalonate **8d** proceeded to 100% conversion, the diester **1d** was inert under these reaction conditions, failing to yield adduct **4**. The cyclopropane **10** bearing only a single carboxylic acid moiety (and no ester) also failed to undergo reaction to produce **11**. Lowering the number of equivalents of the indole to 1.2 lowered the conversion to 50% over the 48 h reaction period. Elevation of the temperature to 50 °C at 13 kbar drastically reduced the reaction time from 48 to 1 h (entries 4 and 8). These conditions also allowed for the lowering of the indole stoichiometry from 2 to 1.2 equiv, without sacrifice of the conversion or yield, thus obtaining the optimal conditions (entry 9).

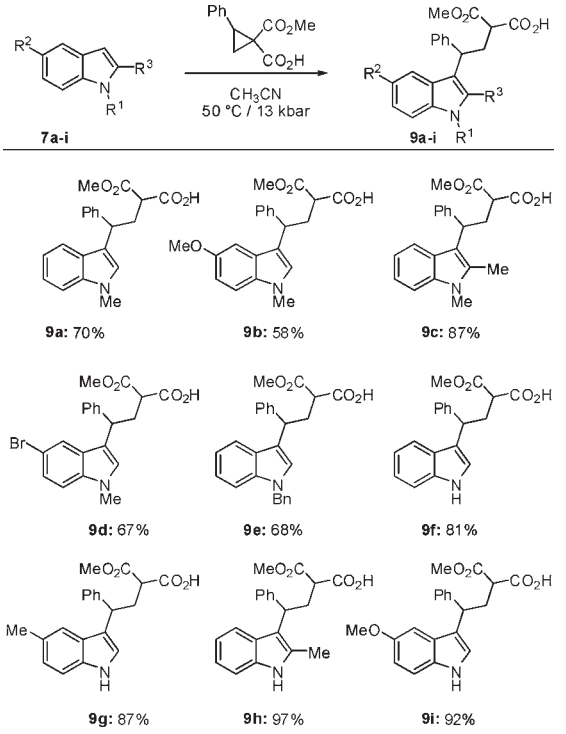



**Figure 2.** Variation of the indole nucleophile.

(5) For reviews on donor−acceptor cyclopropanes, see: (a) Carson, C. A.; Kerr, M. A. *Chem. Soc. Rev.* **2009**, *38*, 3051. (b) Rubin, M.; Rubina, M.; Gevorgyan, V. *Chem. Rev.* **2007**, *107*, 3117. (c) Yu, M.; Pagenkopf, B. L. *Tetrahedron* **2005**, *61*, 321. (d) Reissig, H.-U.; Zimmer, R. *Chem. Rev.* **2003**, *103*, 1151. (e) Wong, H. N. C.; Hon, M. Y.; Tse, C. W.; Yip, Y. C.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165. (f) Danishefsky, S. *Acc. Chem. Res.* **1979**, *12*, 66.

(6) Asano, T.; le Nobel, W. J. *Chem. Rev.* **1978**, *78*, 411.

(7) Kotsuki, H.; Hayashida, K.; Shimanouchi, T.; Nishizawa, N. *J. Org. Chem.* **1996**, *61*, 984.

With optimized conditions in hand (Table 1, entry 9), we subjected cyclopropane **8d** to a reaction with a variety of indoles (Figure 2). The reaction was tolerant of substitution on the indole to a large extent. The fact that 5-methoxyindole **7b** gave modest yields may be attributed to its innate instability. Perhaps the most important observation is that the indoles which had no N-substituent gave higher yields than the substituted examples. We are, at this time, unsure of the reason for this. Not surprisingly, *t*-Boc derivatization of the indole nitrogen attenuated the nucleophilicity such that no reaction was observed. The presence of a methyl group at the 2-position was beneficial, presumably due to its ability to enhance the stability of the iminium ion intermediate (see compound **3** in Figure 1). The presence of a methyl group at the 3-position was not tolerated.

Using indole itself as the nucleophile, we commenced a study of the cyclopropane scope using the hemimalonates **8a**–**k** (Figure 3), prepared via simple monosaponificaiton in methanolic sodium hydroxide.[8] In addition to preparing the cyclopropane **8a** with no additional substituent, we were able to efficiently prepare a variety of cyclopropanes vicinally (with respect to the geminal dicarbonyl moiety) substituted with alkyl, aryl, heteroaryl, and vinyl groups. The hydrolysis of the ester *trans* to the vicinal cyclopropyl substituent is sufficiently more rapid than the *cis*-disposed ester so as to allow not only clean monosaponification but also a reasonable diastereoselection (inconsequential in the context of this work).

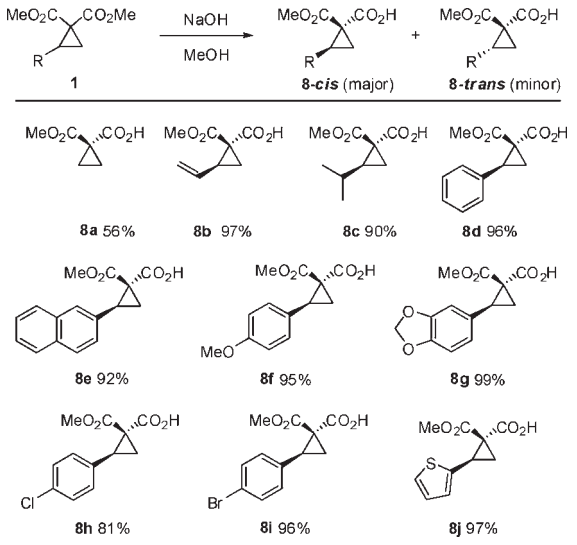



**Figure 3.** Monosaponification of cyclopropane diesters.

In the nucleophilic ring-opening event, aryl and heteroaryl substitution of the cyclopropane was well-tolerated and resulted in the production of the expected adducts in good yields (Figure 4). Cyclopropane **8b** underwent substantial polymerization. Alkyl-substituted cyclopropane **8c** as well as the parent cyclopropane **8a** failed to undergo reaction under these conditions. This is in line with the necessity of the cyclopropane to bear a group capable of stabilizing a developing positive charge in the putative transition state.

The fact that this reaction proceeds in the absence of a Lewis acid catalyst was initially surprising to us. Our supposition is that the presence of a carboxylic acid moiety allows for the formation of a favorable hydrogen bond (Figure 5). It is tempting to assume that this hydrogen bonding enhances the electron-withdrawing ability of the ester moiety (thus facilitating the ring-opening reaction by nucleophiles); however, this would come at the expense of depositing an equal amount of electron density on the carboxylate moiety (making it less electron-withdrawing). Simply stated, the net activation should be close to zero. A more likely reasoning for the increased reactivity of the hemimalonates is that the hydrogen bond stereoelectronically aligns the two carbonyl groups to receive electron density in the ring-opening event. The zwitterion resulting from cyclopropane ring opening would be a highly delocalized 6-electron species.

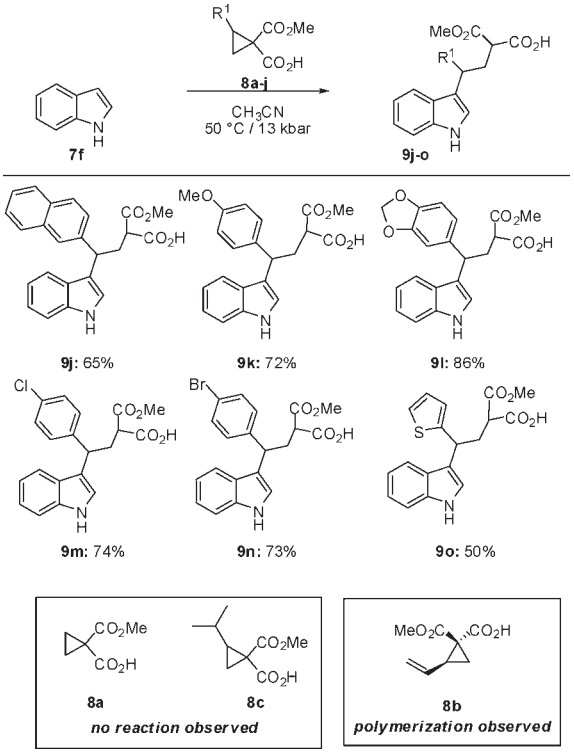



**Figure 4.** Variation of the cyclopropane electrophile.

While it is not surprising that hyperbaric conditions facilitate the nucleophilic ring-opening reaction, it is unusual that the reactions do not occur under conventional thermal conditions. In the Lewis-acid-catalyzed reactions of cyclopropane diesters, thermal conditions are quite effective. We postulate, then, that high pressures *induce*

(8) Perreault, C.; Goudreau, S. R.; Zimmer, L. E.; Charette, A. B. *Org. Lett.* **2008**, *10*, 689.

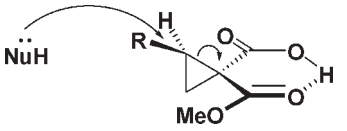



**Figure 5.** Intramolecular hydrogen bond forces coplanarity of the hemimalonate carbonyls.

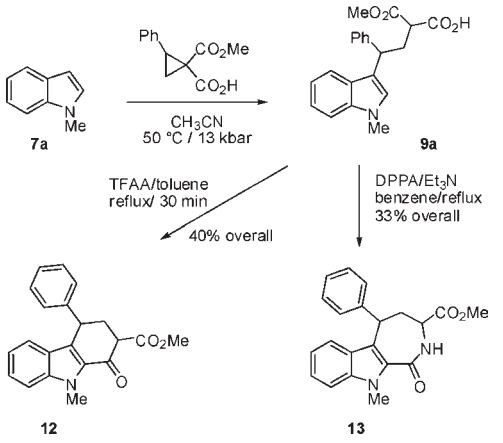
the required hydrogen bonding situation. Efforts are ongoing to support this postulate by calculating molar volumes of the various putative hydrogen-bonded (and non-hydrogen-bonded) species. This may not be as simple as it may seem at first blush. Upon hydrogen bond formation, there will likely be an electrostriction by the surrounding solvent. This effect can often lead to significant reductions in system volume.[9] Thus the solvent and pressure effects may complicate the task of computational modeling. We continue, however, to seek computational methods to address this.

Finally, to show the potential utility of the indolyl hemimalonates, a representative adduct **9a** was subjected to Friedel–Crafts and Curtius reaction conditions (Scheme 1). In the first case, the crude reaction mixture containing **9a** was treated with TFAA in refluxing toluene to produce tetrahydrocarbazole **12** in 40% overall yield from cyclopropane **8d**. When the crude **9a** was treated with DPPA in refluxing benzene, a Curtius rearrangement ensued, followed by trapping of the isocyanate by the nucleophilic indole to form the azepinoindole **13** in 33% overall yield from **8d**.

In summary, we have shown the first nucleophilic ring-opening reactions of cyclopropane hemimalonates. The reaction is facilitated by the enforcement of an intramolecular hydrogen bond under hyperbaric conditions. This obviates the need for the Lewis acid catalyst normally required for such reactivity. The high pressure conditions allow for the suppression of decarboxylation, allowing maintenance of the carboxylic acid moiety. The resulting adducts are intermediates for elaboration to other useful species. Further exploration of this mode of cyclopropane activation is underway.

(9) Klärner, F.-G.; Diedrich, M. K.; Wigger, A. E. Effect of Pressure on Organic Reactions. In *Chemistry under Extreme or Non-classical Conditions*; van Eldik, R., Hubbard, C. D., Eds.; Wiley: New York, 1997; pp 109–110.

**Scheme 1.** Elaboration of the Adducts

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**Supporting Information Available.** Full experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.