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# Direct Functionalization of Indoles: Copper-Catalyzed Malonyl Carbenoid Insertions

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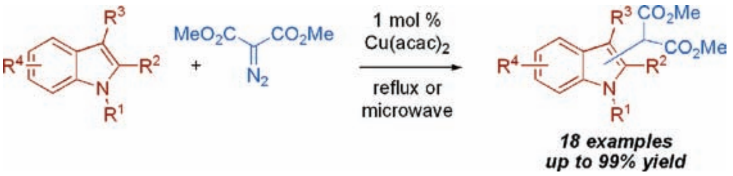
## ABSTRACT



***18 examples***
***up to 99% yield***

**Indoles, when treated with dimethyl diazomalonate under catalysis by Cu(acac)$_2$, undergo C−H insertion reactions regioselectively depending on the substitution pattern on the indole moiety. Indoles where the 3-position is substituted give high yields of the C2−H insertion product. Microwave conditions are also disclosed which show comparable yields with reduced reaction times.**

Indole derivatives permeate pharmaceutical, agrochemical, and functional material sciences, and as such the development of mild, selective, and efficient derivatization protocols for the synthesis of useful indoles remains a burgeoning field of synthetic research.[1] Effective C−H bond activation and transition metal catalyzed cross coupling reactions continue to grow in prominence as proficient modes of derivatization, often excelling in efficiency.[2] Since the early investigations[3] on the decomposition of α-diazo esters to generate carbenes or metal-stabilized carbenoids, their reactivity with indoles has garnered attention as a unique method of functionalization.[4] More recently Qin has demonstrated the capability of this mode of reactivity in the synthesis of a number of

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impressive natural products.[5] Herein, we report an economical, high yielding, and technically simple method for the installation of a malonyl unit on the pyrrole portion of the indole ring system.

In 2002 we disclosed the reaction of dimethyl diazomalonate **6** with a variety of indoles under dirhodium tetraacetate catalysis to give N1, C2, or C3 malonyl indoles, depending on original substrate substitution patterns.[6] Our interest in this type of reaction was driven by a desire to access, by total synthesis, indole natural products bearing an acetyl (or malonyl) moiety at the indole 2-position. Figure 1 illustrates some representative compounds which have piqued our interest.

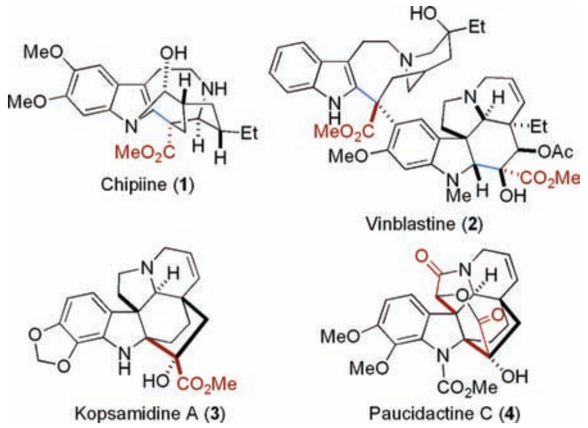


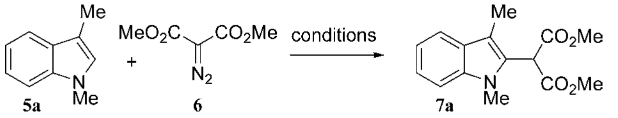
**Figure 1.** Indole natural products containing a **2** and/or **3** acetate moiety.

In addition to their presence in natural products, the 2-malonyl indole has been integral as an important intermediate as demonstrated by total syntheses completed by Overman[7] and Fukuyama.[8] They have also appeared in biosynthetic proposals of natural products.[9]

At the outset of our 2002 study, a few limitations became clear. While the reaction excelled at the installation of a malonate moiety in the 3-position of unsubstituted indoles, moderate or low yields were obtained from 2- and 3-substituted indoles to give the corresponding 3- or 2-malonyl indoles, respectively.

We commenced our study by screening reaction conditions for the carbenoid insertion of dimethyl diazomalonate **6** into the 2-position of *N*-methyl skatole **5a**. We selected this indole substrate since we expected C2 insertion to be the more difficult process (with respect to C3 insertion) and an optimal set of conditions with this substrate would likely excel at the more facile C3 insertion. The results are summarized in Table 1. Conditions adapted from our original study (entry 1) gave moderate amounts of **7a** after 7.5 h. Substituting copper catalysts known to promote carbenoid formation gave no desired product after extended reaction times at room temperature (entries 2 and 3).[10]

**Table 1.** Optimization Studies



| entry | solvent | temp | time | catalyst (mol %) | **6**:**5a** | **7a**[a] |
|---|---|---|---|---|---|---|
| 1 | $CH_2Cl_2$ | rt | 7.5 h | $Rh_2(OAc)_4$ (10) | 1:1 | 37% |
| 2 | $CH_2Cl_2$ | rt | 24 h | $Cu(acac)_2$ (10) | 1:1 | NR |
| 3 | $CH_2Cl_2$ | rt | 24 h | $Cu(OTf)_2$ (10) | 1:1 | NR |
| 4 | toluene | reflux | 1 h | $Cu(OTf)_2$ (10) | 1:1 | ND[b] |
| 5 | toluene | reflux | 40 min | $Cu(acac)_2$ (10) | 1:1 | 64% |
| 6 | benzene | reflux | 75 min | $Cu(acac)_2$ (10) | 1:1 | 75% |
| 7 | benzene | reflux | 2 h | $Cu(acac)_2$ (5) | 1:1 | 76% |
| 8 | benzene | reflux | 6 h | $Cu(acac)_2$ (1) | 1:1 | 82% |
| 9 | benzene | reflux | 4 h | $Cu(acac)_2$ (1) | 1:2 | 90% |
| 10 | benzene | reflux | 6 h | $\mathbf{Cu(acac)_2}$ (1) | 1:1.5 | 88% |

[a] Yield of isolated products. [b] Yield not determined. Complex mixture resulted with **7a** as a minor component as observed by $^1$H NMR.

When more vigorous reaction conditions were employed (entries 4 and 5) the copper catalysts began to display reactivity in carbenoid formation and C2−H insertion in reduced reaction times, though $Cu(OTf)_2$ (entry 4) provided an intractable mixture of compounds with **7a** formed in small amounts. Entry 5 showed the most promise with $Cu(acac)_2$ providing **7a** in the highest yield observed thus far. By utilizing a lower boiling solvent (entry 6) a moderate increase in yield was again observed.

Decreasing the catalyst loading to 1% provided another increase in yield of **7a** to 82% with only a slight increase in reaction time. Upon adjusting the ratio of dimethyl diazomalonate **6** to *N*-methyl skatole **5a** to 1:2 a maximum yield of **7a** was observed. Adjusting the ratio of the indole component once more showed negligible change in the reaction, and we chose these conditions as optimal for the insertion of the malonyl carbenoid into the C2−H position of 3-substituted indoles (entry 10).

With optimal conditions in hand, we surveyed indole substrates which bore substitution at the various positions of the indole ring system (Table 2). We first examined the effects of substitution at the 2- and 3-positions (indole numbering) and were pleased to find, in general, that the new conditions provided the desired malonyl indoles in greatly increased yields in comparison to those previously observed by us. The lowest yield (while still acceptable) was observed for a substrate bearing an electron-withdrawing

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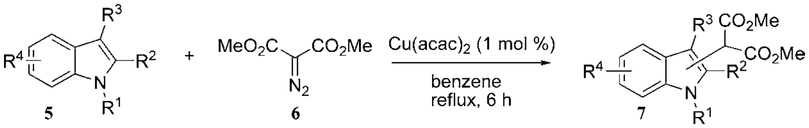
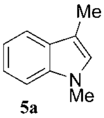
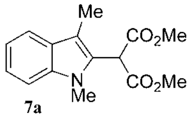
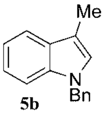
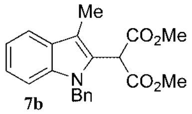
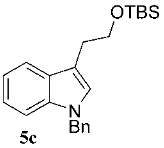
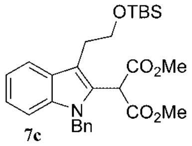
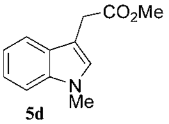
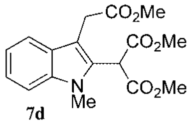
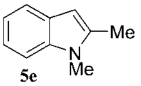
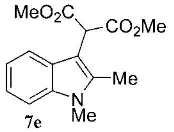
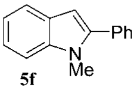
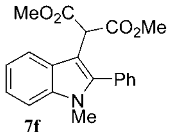
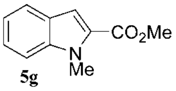
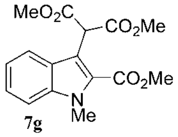
**Table 2.** Scope of Malonyl C−H Insertion



| entry | substrate | product | yield[a] |
|---|---|---|---|
| ***Effects of 2- or 3-substitution*** | | | |
| 1 |  5a |  7a | 88 |
| 2 |  5b |  7b | 89 |
| 3 |  5c |  7c | 78[b]<br>81[c] |
| 4 |  5d |  7d | 83 |
| 5 |  5e |  7e | 99 |
| 6 |  5f |  7f | 93 |
| 7 |  5g |  7g | 60 |
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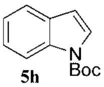
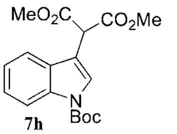
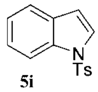
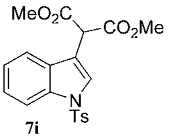
| 8 |  5h |  7h | 68 |
| 9 |  5i |  7i | 45 |
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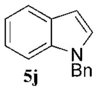
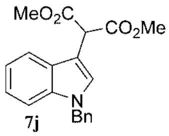
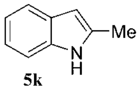
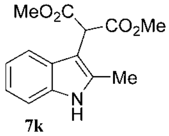
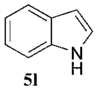
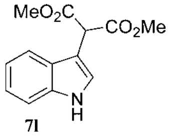
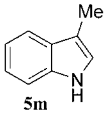
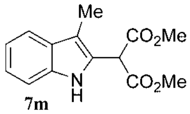
| 10 |  5j |  7j | 98 |
| 11 |  5k |  7k | 81 |
| 12 |  5l |  7l | 80 |
| 13 |  5m |  7m | 87 |
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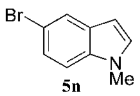
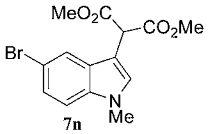
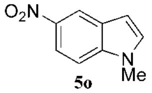
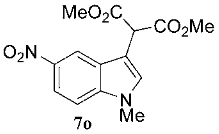
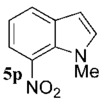
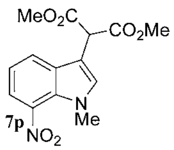
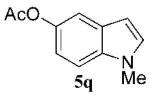
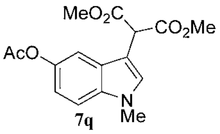
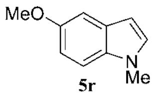
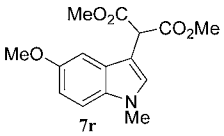
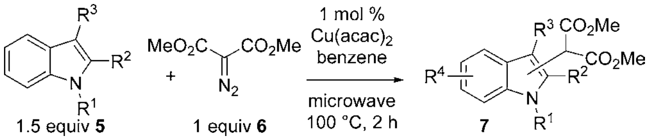
| 14 |  5n |  7n | 96 |
| 15 |  5o |  7o | 79 |
| 16 |  5p |  7p | 94 |
| 17 |  5q |  7q | 55 |
| 18 |  5r |  7r | 95 |

[a] Yield of isolated products. [b] Reaction run on 0.6 mmol scale. [c] Reaction run on 8.7 mmol scale.

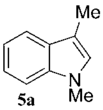
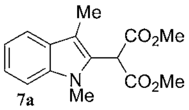
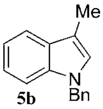
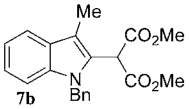
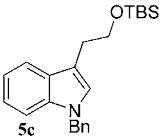
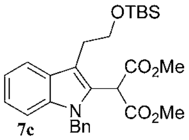
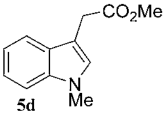
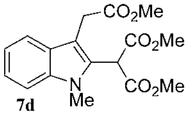
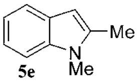
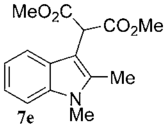
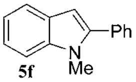
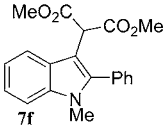
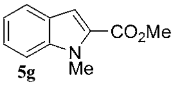
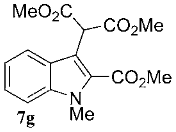
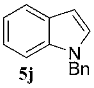
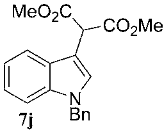
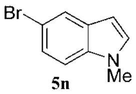
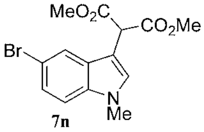
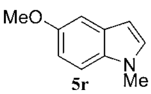
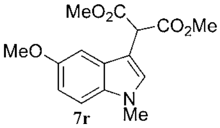
ester moiety at the 2-position (entry 7). This is likely due to the attenuated reactivity of the electron-poor indole toward the electrophilic carbenoid.

Next, the effects of N-substitution were examined. Surprisingly, *N*-tosyl and *N*-Boc indole (entries 8 and 9) gave appreciable yields of products. This may be considered

**Table 3.** Microwave-Promoted C−H Insertions



1.5 equiv **5** + 1 equiv **6** → **7**

| entry | substrate | product | yield[a] |
|---|---|---|---|
| 1 |  **5a** |  **7a** | **85%** |
| 2 |  **5b** |  **7b** | **87%** |
| 3 |  **5c** |  **7c** | **69%** |
| 4 |  **5d** |  **7d** | **70%** |
| 5 |  **5e** |  **7e** | **69%** |
| 6 |  **5f** |  **7f** | **79%** |
| 7 |  **5g** |  **7g** | **48%** |
| 8 |  **5j** |  **7j** | **93%** |
| 9 |  **5n** |  **7n** | **91%** |
| 10 |  **5r** |  **7r** | **93%** |

[a] Yield of isolated products.

unusual since N-tosylation greatly limits the nucleophilic reactivity of indoles. As expected substitution occurs at the 3-position of the indole where possible (entries 8−12); however, in cases where this position is occupied, 2-subsitution occurs in a facile fashion (entry 13). It is interesting to note that in contrast to our previously reported Rh-catalyzed process where N−H insertion was a major product when unprotected skatole was the substrate, little N-substitution was observed under the present copper-catalyzed conditions (entry 13).[11]

Substitution on the benzenoid portion of the indole was surprisingly well tolerated in most cases. Both electron-withdrawing (entries 14−16) and electron-donating moieties (entries 17 and 18) were well behaved. The low yield observed for entry 17 is anamolous, but greater than 85% of the unreacted indole starting material could be recovered from the reaction, suggesting that multiple reaction cycles could provide higher yields.[12]

In an effort to decrease reaction times, we explored the carbenoid insertion reaction under microwave irradiation conditions. By adjusting the reaction temperature to 100 °C and employing microwave conditions we found that the desired malonyl indoles could be obtained in comparable yields in only 2 h (Table 3).

In summary, we have developed conditions for the Cu(acac)$_2$-catalyzed malonyl carbenoid insertion into indole substrates, which excels for a variety of substitution patterns and functional groups. The reaction proceeds with a high degree of regiocontrol and can be accelerated under microwave irradiation conditions. Applications of this reaction in total synthesis endeavors are currently underway in our laboratories, and will be presented in due course.

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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.

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(11) Less than 10% N−H carbenoid insertion as observed by $^1$H NMR.

(12) 85% recovered **5q** based on expected return, given 55% **7q** isolated.