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Convenient Preparation of Indolyl Malonates via Carbenoid Insertion

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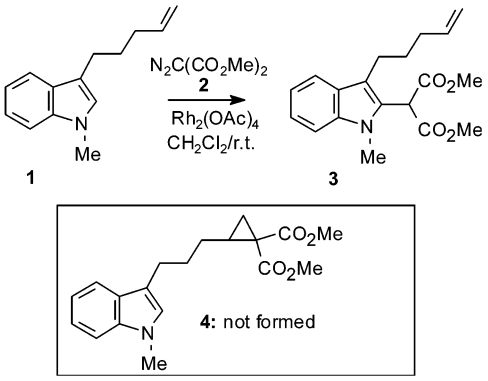
Abstract: Indoles, when treated with methyldiazomalonate under catalysis by rhodium(II)acetate, undergo C−H and N−H insertion reactions regioselectively depending on the substitution pattern on the indole moiety. In indoles where the 3-position is unsubstituted, high yields of the C3−H insertion product were observed. In 3-alkylindoles, 2-substitution predominated, while *N*-methyltetrahydrocarbazole yielded the product resulting from insertion into the C6−H bond. Indoles in which the nitrogen is unprotected yield varying degrees of N−H insertion.

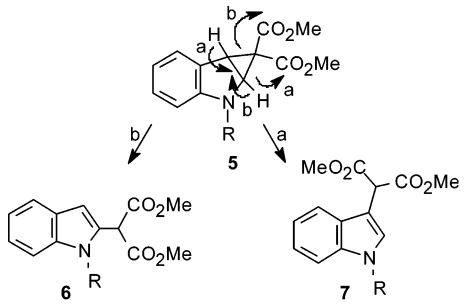
The indole moiety remains at the forefront of biological and medicinal chemistry. The most ubiquitous of the bioactive alkaloids known are based on the indole nucleus.[1] Medicinal chemists repeatedly turn to indole-based compounds as a target pharmacophore for the development of therapeutic agents.[2] It should come as no surprise, then, that there continues to be considerable emphasis on new methods for the formation and the elaboration of the benzopyrrole ring system.[3] Such methods add to the palette of the synthetic chemist and aid in the chemical synthesis of indole alkaloids.[4] For some time now, our group has been keenly interested in the development of new methods for the formation[5] and the elaboration[6] of the indole ring system.

During the course of a study of intramolecular indole/cyclopropane cyclopentannulations,[6b,d] we had occasion to attempt the preparation of cyclopropane **4** via the treatment of olefin **1** with methyldiazomalonate **2** in the presence of catalytic rhodium acetate (Scheme 1).[7] The only identifiable reaction product was not the desired cyclopropane but the malonic ester **3**. This type of reaction is not without precedent[8] and could proceed via a cyclopropylindoline,[8a] which collapses rapidly to the observed alkylated indole. Most of the reported cases of this type of reaction are intramolecular, and no reports appear to exist for the general reaction of diazomalonates with indoles. Herein we report a useful and high-yielding method for the installation of a malonate moiety into the 3-position of indoles.

SCHEME 1



SCHEME 2



While Scheme 1 shows an alkylation at the 2-position of the indole moiety, the putative intermediate **5** could conceivably collapse to two regioisomeric products giving either the 2-alkyl or 3-alkyl product (Scheme 2). Loss of a proton from the benzylic position and dissociation of the cyclopropane bond leads to 3-alkylation (compound **7** via path a). Loss of a proton α to the nitrogen atom and dissociation of a cyclopropane bond leads to 2-substitution (compound **6** via path b). Existing substitution

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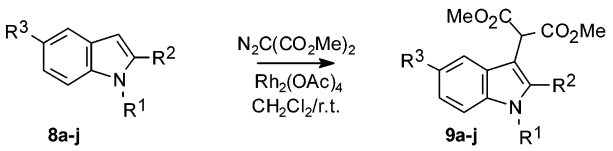
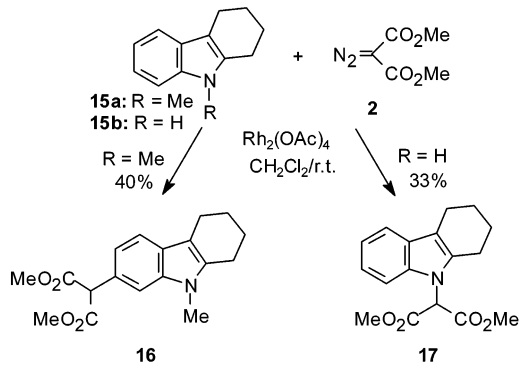
TABLE 1. Reaction of Indoles with Dimethyldiazo Malonate



entry	R^1	R^2	R^3	time	yield (%)
a	Me	H	H	1.5	96
b	Me	H	Br	1.5	91
c	Me	H	OMe	1.5	85
d	Bn	H	H	1.5	78
e	TIPS	H	H	1.5	84
f	Ts	H	H	12	31
g	Me	Me	H	1.5	67
h	Me	Ph	H	12	44
i	Me	CH_2OMe	H	12	38
j	H	Me	H	12	43

SCHEME 3

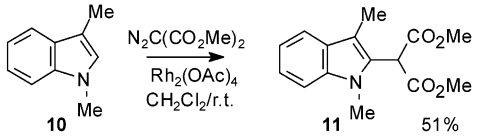


on the indole C-3-position would preclude path a and force 2-alkylation, while existing substitution at C-2 would preclude path b and force 3-alkylation. In unsubstituted indoles, 3-alkylation should be favored since one can invoke participation by the nitrogen lone pair in the stabilization of a developing positive charge in the transition state of path a.[9]

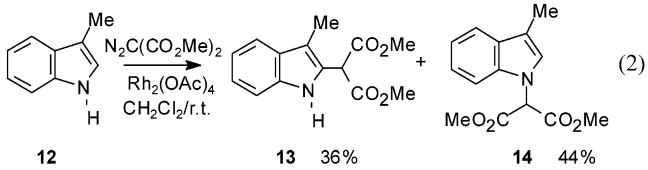
Table 1 summarizes the results of a study in which a variety of indole substrates were reacted with dimethyldiazo malonate under the influence of catalytic rhodium acetate. Several points are worthy of note from Table 1. For indoles, which bear simple substitution on the benzenoid portion, the yields are uniformly high and the reactions extremely clean (entries a−e). Substitution at the 2-position is tolerated; however, the yields are slightly diminished. This may in part be due to the electron-withdrawing nature of some of the substituents. In fact, *N*-methyl-2-carbomethoxyindole failed to react. Tosylation of the nitrogen atom of the indole ring system also leads to reduced yields. In most cases, the yields in Table 1 represent synthetically useful transformations. It is worth drawing attention to the fact that the coupling of the electron-rich 3-position of the indole moiety to the inherently nucleophilic central carbon of the malonic ester represents an umpolung transformation that would be otherwise difficult to accomplish.

(9) It should be noted that the formation of a cyclopropyl intermediate is far from certain, and the reaction may simply be a direct C−H insertion reaction. Low-temperature NMR studies were suggestive of a cyclopropylindoline but far from conclusive.

It is apparent from Table 1 that the preferential regiochemical outcome in 2,3-unsubstituted indoles is 3-subsitution. We were curious as to whether 2-substitution could be forced and, if so, with what efficiency. 1,3-Dimethyl indole **10** and 3-methylindole **12** (skatole) were subjected to the reaction conditions used in Table 1 (eqs 1 and 2, respectively). The reaction times were longer and the yields lower; however, substitution did take place at the 2-position yielding **11** (from **10**) and **13** (from **12**). The N-substituted product **14** (separable from **13** by column chromatography) was formed as the major product in this case.



(1)



(2)

If positions 1−3 were all substituted, insertion took place at the 6-position (indole numbering). When *N*-methyl tetrahydrocarbazole **15a** was treated under the usual conditions, **16** was produced in 40% yield (Scheme 3).[10] In the analogous compound with the nitrogen atom unprotected (**15b**), insertion took place at the N−H bond to form **17** in 33% yield.

During the course of our studies, it occurred to us that the observed transformation could simply be a Lewis acid-catalyzed process. It is worth noting, then, that a variety of Lewis acids ($ZnCl_2$, $BF_3{\cdot}Et_2O$, Bu_2OTf, and $YbOTf_3{\cdot}2H_2O$) failed to yield identifiable products. Other catalysts presumably capable of carbenoid chemistry (such as the rhodium(II) trifluoroacetate dimer and copper triflate) also failed to produce product. The absence of any catalyst resulted in the recovery of starting materials.

In summary, we have disclosed a useful and technically simple method for the installation of a malonic ester moiety at the 3-position of indoles. This promises to be a useful addition to the synthetic toolbox of the synthetic indole chemist.

Experimental Section

General Considerations. All reactions were performed in anhydrous dichloromethane (except where indicated). The reagents used were purchased commercially. TLC analysis was performed using silica gel 60 F_{254}. Diazomalonate was prepared from malonate and 4-acetamidobenzenesulfonyl azide in acetonitrile. Products were purified by flash chromatography using silica gel (230−400 mesh).

Melting points are uncorrected. IR spectra were recorded as thin films on NaCl plates. NMR experiments were performed at 400 MHz, and spectra were obtained in $CDCl_3$. Mass spectra were obtained at an ionizing potential of 70 eV.

(10) Compelling evidence for the regiochemistry of **16** (5- vs 6-substitution) was provided by HMBC and HSQC NMR correlation experiments. The reason for the regiochemistry is not yet understood.

Typical Experimental Procedure: **Dimethyl (1-Methyl-1*H*-indol-3-yl)malonate (9a).** To a solution of 1-methylindole (**8a**) (113 μL, 0.88 mmol) and $Rh_2(OAc)_4$ (15 mg, 0.03 mmol) in CH_2Cl_2 (5 mL) at 23 °C was added diazomalonate (284 mg, 0.17 mmol) dissolved in CH_2Cl_2 (5 mL) via cannula. After 1.5 h, the reaction mixture was filtered through Celite and washed with CH_2Cl_2. The crude mixture was then preabsorbed on silica gel and subjected to flash chromatography using a gradient elution technique (from 2.5 to 15% EtOAc in hexanes) to afford **9a** (223 mg, 0.85 mmol, 96%) as a white solid: mp 98−99 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (dd, J = 8.4, 0.8 Hz, 1H), 7.28 (m, 3H), 7.16 (m, 1H), 5.00 (s, 1H), 3.78 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) 169.2, 136.8, 128.8, 127.1, 122.2, 199.8, 199.2, 109.7, 105.7, 53.2, 49.5, 33.3; IR (thin film) ν 1747, 1737 cm^{-1}; EI-HRMS for $C_{14}H_{15}NO_4$ found 261.1003, calcd 261.1001.

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Supporting Information Available: Complete experimental procedures as well as ^{1}H NMR, ^{13}C NMR, IR, and MS data for compounds **3**, **9a**−**j**, **11**, **13**, **14**, **16**, and **17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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