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LETTERS

The annulation of 3-alkylindoles with 1,1-cyclopropanediesters

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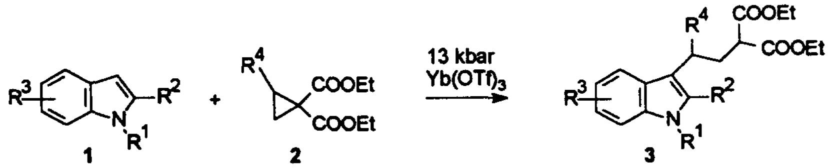
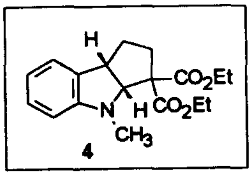
Abstract

A variety of indoles, all bearing a methyl group in the 3-position, underwent smooth reaction with 1,1-cyclopropanediesters to yield annulated adducts in fair to excellent yield. Under kinetic control the annulation reaction was dominant, but under high temperature conditions for extended periods of time, rearrangement occurred leading to 2,3-dialkylindoles. Hyperbaric conditions were found to be effective in sterically demanding cases.

Recently we reported a novel reaction in which indoles **1** bearing only a hydrogen at the 3-position acted in a nucleophilic manner in the ring-opening of a variety of 1,1-cyclopropanediesters **2**, resulting in the formation of a series of 2-carboalkoxy-4-indolylbutanoate esters **3**.[1] During the course of this study, a byproduct **4** was isolated in trace amounts.





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The formation of **4** presumably arises from attack of the intermediate malonic enolate on the iminium moiety in **5** in a competitive process with deprotonation (path a) and rearomatization of the benzopyrrole to give indole **6**. We were intrigued by this hypothesis and speculated that the presence of a non-hydrogen at the 3-position of the indole would lead to **7** via the annulation (path b) as the only reasonable course of reaction. This is reminiscent of annulation observed when 3-alkyl indoles react with α,β-unsaturated ketones.[2] This letter describes our preliminary results.

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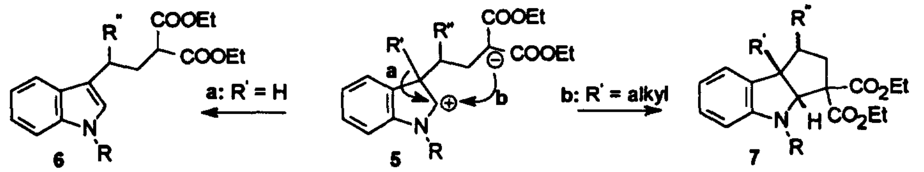
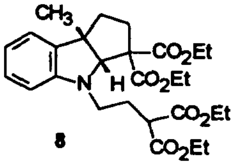


Skatole (3-methylindole) seems to possess the minimum structural requirements for nucleophilic participation in the annulation process; a non-hydrogen substituent at C-3. While the annulation reaction took place (~65%), it was accompanied by attack on a second equivalent by alkylation of the newly nucleophilic indoline nitrogen atom to form adducts such as **8**. Since we were primarily interested in studying the annulation process, we chose indoles **9–11** since they were readily available and possessed an *N*-alkyl substituent (preventing the formation of adducts such as **8**). Cyclopropanes **12–15** were used as the electrophilic partners since they were easily prepared by treatment of alkylidene malonates with dimethylsulphoxonium methylide.[3]



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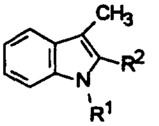
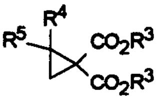


9: R^1=Me, R^2=H
10: R^1=Me, R^2=Me
11: R^1=Bn, R^2=H



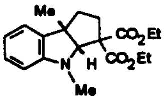
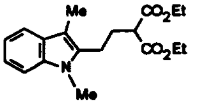
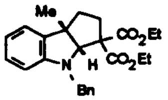
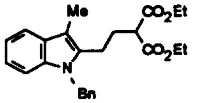
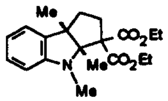
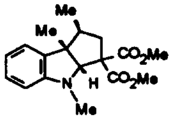
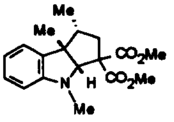
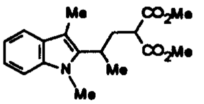
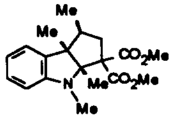
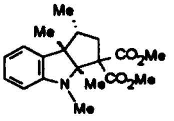
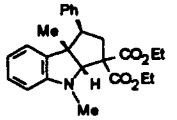
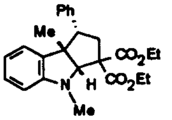
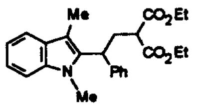
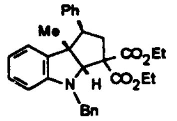
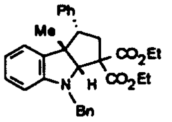
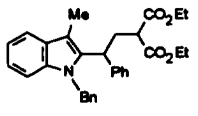
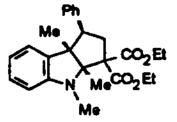
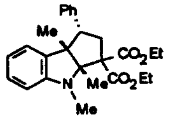
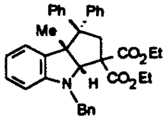
12: R^3=Et, R^4=R^5=H
13: R^3=Et, R^4=Ph, R^5=H
14: R^3=Me, R^4=Me, R^5=H
15: R^3=Et, R^4=R^5=Ph

After a brief optimization study involving indole **9** and cyclopropane **12**, suitable reaction conditions (solvent, catalyst loading, stoichiometry and temperature) were developed.[4] Table 1 summarizes the results of the reaction of indoles **9–11** with cyclopropanes **12–15**.[5] Although some of the yields seem modest (40–50%), this belies the clean nature of the reactions. The lower than expected yields are primarily due to competitive decomposition/polymerization of the cyclopropane which was used as the limiting reagent. Use of an excess of the cyclopropane did not improve the yields. Isolation of gram quantities of the annulation product was routine. The products were observed (by X-ray diffraction) to have a *cis*-ring fusion with the two five-member rings at an angle of 109°. Not surprisingly, the nature of the alkyl group on the nitrogen atom of the indole did little to affect the course of the reaction. The presence of a methyl group at C-2 was also tolerated, however, the increased steric demands required that hyperbaric conditions be employed.

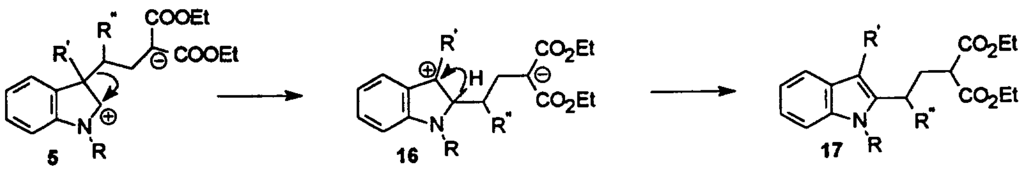
Based on our previous work[1] on reactions where the cyclopropane diester bore additional substitution at one of the carbons (**13–15**), nucleophilic attack occurred exclusively at the substituted carbon. In the case of **14**, the products were formed with little or no diastereoselection, however, in the case of the phenyl-substituted cyclopropane **13**, reasonably good selectivity was noted. In the case of entry 7, the diastereomeric ratio could be improved to 30:1 after a single recrystallization. The major isomer had the phenyl group *anti* to the angular methyl group and in an *endo* relationship in the bent ring system.

Although in general, the annulation products were the only compounds isolated, when the reaction conditions involved the use of higher temperatures, a byproduct (e.g. **17**) was isolated in significant amounts. These compounds presumably arose via the migration of the newly installed alkyl chain in intermediate **5** to produce a 3° benzylic carbocation **16**, which subsequently rearomatized to the benzopyrrole by loss of a proton. As expected, the migratory aptitude of the alkyl chain was greater than the C-3 methyl group. In the cases where the migrating ability was expected to be the greatest (entries 6 and 7), the yields of the rearrangement product were correspondingly high and provided a striking example of kinetic versus thermodynamic control. The fact that this is a migration and not a direct alkylation of the C-2 position of the indole has been addressed.[6]

Table 1
Results of the reaction of indoles 9–11 with cyclopropanes 12–15

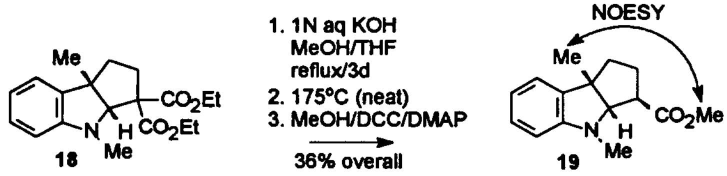
Entry	Indole	Cyclopropane	Conditions[a]	Annulation Product (yield)	Rearrangement Product (yield)
1	9	12	120°C/1d[b] reflux/2d 13 kbar/7d	 (41) (37) (39)	 (5) (6) (5)
2	11	12	reflux/2d	 (42)	 (5)
3	10	12	13 kbar/7d	 (43)	
4	9	14	reflux/7d 13 kbar/7d	  (27) (48) β:α = 1:1	 (15) (8)
5	10	14	13 kbar/7d	  (32) β:α = 1:2	
6	9	13	r.t/4h reflux/7d	  (89) (0) β:α = 1:5	 (<5) (51)
7	11	13	r.t/4h reflux/3d	  (94) (trace) β:α = 1:8	 (<5) (76)
8	10	13	r.t/1d	  (62)	
9	11	15	reflux/10h	 (45)	

[a] All reactions were performed in acetonitrile in the presence of 5 mol% Yb(OTf)$_3$. [b] The reaction was performed in a sealed tube.



The diesters could be saponified and subjected to thermal decarboxylation. For example, when **18** was treated with aqueous KOH in methanolic THF, smooth conversion to the diacid occurred. Heating the crude diacid produced a monoacid which was converted to the methyl ester and isolated as a single diastereomer. Examination of the NOESY spectrum of **19** indicated that the methyl ester was *exo* to the tricyclic ring system.

In summary, we have developed a novel annulation procedure for the formation of pentannulated indolines with a unique molecular scaffolding. Future work will involve the preparation of these compounds in homochiral form, either by using optically pure cyclopropanes,[7] or by resolution of the adducts. Conversion of the enantioenriched adducts to novel β-amino acids for use in peptidomimetics,[8] or to the corresponding amino alcohols for use as chiral ligands for asymmetric borane reductions will also be explored.[9] Results of our research in this area as well as a detailed discussion of the work described herein will be reported in due course.



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4. General conditions are as follows: **Ambient pressure** — the indole (2 equiv.), cyclopropane (1 equiv.) and Yb(OTf)$_3$ (5 mol%) were weighed into a dry reaction vessel, equipped with a stirring bar. The vessel was then purged with argon under a septum seal. Acetonitrile was added via syringe and the mixture stirred for the indicated period of time at either room temperature, reflux or in a sealed tube. When TLC analysis of the reaction mixture indicated that the reaction progress had ceased, the mixture was brought to ambient temperature and the solvent was removed in vacuo. The residue was purified by flash chromatography on silica gel using mixtures of EtOAc/hexane as the eluant. **High pressure** — the reaction mixture was prepared as in Method A and was transferred to a length of heat shrinkable teflon tubing which was sealed at one end with a brass clamp. Excess air was squeezed from the tubing and it was sealed with a second clamp. The tubing was inserted into the high pressure reactor and the pressure increased to 13 kbar. After the indicated period of time, the reactor was depressurized and the reaction mixture transferred to a round-bottomed flask and worked up in the usual way.
5. All compounds exhibited analytical data consistent with the proposed structures. Representative data for compound **18** (entry 1 from Table 1) is as follows: mp=65–66°C; R_f=0.32 (10% EtOAc/hexanes); ^{1}H NMR (250 MHz, CDCl$_3$) δ=7.07 (t, *J*=7.6 Hz, 1H), 6.97 (d, *J*=7.3 Hz, 1H), 6.70 (t, *J*=7.6 Hz, 1H), 6.43 (d, *J*=7.9 Hz, 1H), 4.33–4.06 (m, 5H), 2.83 (s, 3H), 2.30–2.18 (m, 1H), 2.11–1.98 (m, 2H), 1.70–1.59 (m, 1H), 1.46 (s, 3H), 1.27 (t, *J*=7.3 Hz, 3H), 1.26 (t, *J*=7.0 Hz, 3H); ^{13}C NMR δ=171.5, 169.0, 152.9, 137.4, 127.9, 122.3, 118.3, 108.5, 82.0, 67.2, 61.3, 61.0, 54.0, 39.0, 38.7, 32.5, 28.6, 14.1 (2 carbons); IR (neat) ν_{max}=3020, 2950, 2925, 2840, 1740, 1715, 1590, 1475 cm^{-1}; MS (EI) *m/z* (%)=332 (17.9, M+1), 331 (100, M$^+$), 286 (9.9), 159 (29.5), 158 (30.1), 144 (45.3); EIHRMS for $C_{19}H_{25}NO_4$, found: 331.1779 amu, requires: 331.1783 amu.

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