COMMUNICATION

Oxocarbons and related compounds. Part 24.[1] Chlorosquarylation of indoles

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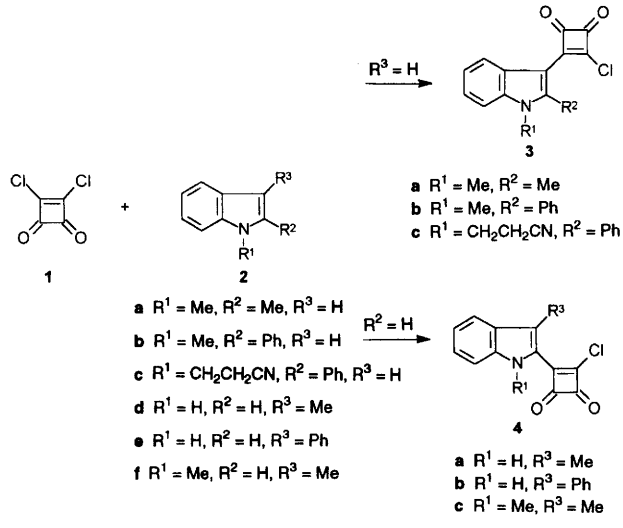
Chlorosquarylated indoles 3 and 4 have been synthesized from indoles 2 and squaric dichloride 1 and have been treated with nitrogen- and oxygen-nucleophiles.

A large number of indoles are distinguished by their biological activity. In particular, specifically substituted indoles serve as the starting material for the synthesis of natural products and also for pharmacologically active compounds.[2] As a consequence, there is a steady demand for novel synthetically versatile indole derivatives. Of fundamental importance in the search for such building blocks is the attachment of a polyfunctional subunit to the indole nucleus, with the capacity to undergo a great many, easy chemical transformations.[3] We intended to achieve this by introducing the 2-chloro-3,4-dioxocyclobut-1-enyl group (chlorosquaryl group) to the indole nucleus. For this purpose we began an investigation into the reaction of 3,4-dichlorocyclobut-3-ene-1,2-dione (squaric dichloride) **1** with indoles.

Though squaric dichloride **1** has been used extensively for the acylation of arenes[4] there is, surprisingly, only one mention in the literature of the extension of this reaction to indoles: a solution of squaric dichloride **1** and 1,2-dimethylindole **2a** (in excess) in dichloromethane was passed through a column of acidic alumina, thus affording 3,4-bis(1,2-dimethyl-3-indolyl)-cyclobut-3-ene-1,2-dione (0.67%).[5]

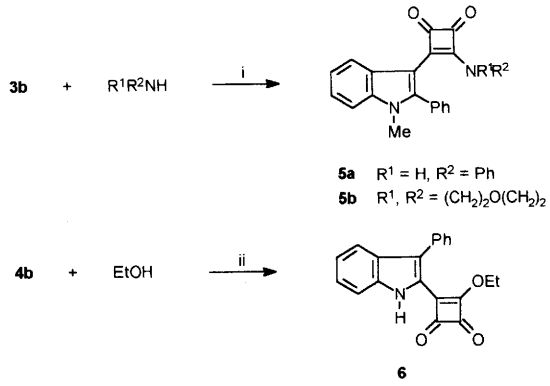
We have found that the reaction of the indoles **2a–f** with squaric dichloride **1** (1 equiv.) in an appropriate solvent affords the chlorosquarylated indoles **3** and **4** (Scheme 1, Table 1).



Scheme 1 Chlorosquarylation of indoles. For conditions see Table 1.

In agreement with reports on the acylation of indoles,[6] chlorosquarylation takes place at C-3 of indoles **2a–c** (Table 1, entries 1–4) with the formation of **3a–c**, and at C-2 of indoles **2d–f** (Table 1, entries 5–7), with the formation of **4a–c**. Depending on their specific substitution patterns, the chlorosquarylated indoles **3** and **4** exhibited different polarity and solubility properties. While **3a–c** and **4c** could be recrystallized easily, this was not the case with **4a** and **4b**. In an attempt to recrystallize **4b** from ethanol, the ethoxysquarylated indole **6** was obtained (*vide infra*).

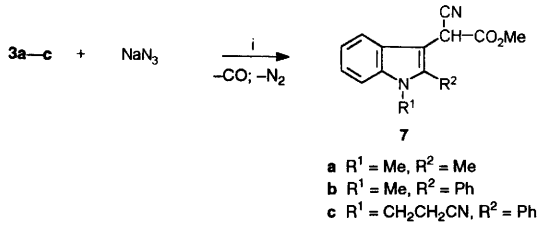
On heating solutions of the chlorosquarylated indole **3b** in EtOH or THF with a primary amine (aniline) and a secondary amine (morpholine) for 30 min the aminosquarylated indoles **5a** and **5b** were obtained (Scheme 2). When **4b** was heated at



Scheme 2 *Reagents and conditions:* i, THF or EtOH, reflux, 30 min; ii, reflux, 3 min

reflux in EtOH for 3 min the ethoxysquarylated indole **6**, 3-ethoxy-4-(1-methyl-3-phenyl-1*H*-indol-2-yl)cyclobut-3-ene-1,2-dione, crystallized from the filtrate in analytically pure form (Scheme 2).

The chlorosquaryl unit's unique range of subsequent valuable synthetic transformations has been further demonstrated by the reaction of the chlorosquarylated indoles **3a–c** with sodium azide in methanol. Accompanied by the evolution of CO and N_2, the methyl indol-3-ylcyanoacetates **7a**[7] (42%), **7b**[7] (71%) and **7c** (66%) were obtained‡ (Scheme 3). It is



Scheme 3 *Reagents and conditions:* i, acetone–MeOH, reflux 15–30 min

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‡ This is an extension of the reaction of 3-halogeno-4-phenylcyclobut-3-ene-1,2-dione with sodium azide. Phenylcyanoketene is generated which, in alcoholic solution, reacts further to give alkyl phenylcyanoacetates.[8]

Table 1 Chlorosquarylation of indoles

Entry	Indole	Solvent and conditions	Time (t/min)	Product[a]	Yield[b] (%)	Mp[c] (T/°C)
1	**2a**	Benzene, rt	45	**3a**	51	163–164 (decomp.)
2	**2b**	Benzene, rt	45	**3b**	26	169–170
3	**2b**	$CHCl_3$, rt	45	**3b**	21	168–169
4	**2c**	Benzene, reflux	120	**3c**	39	201–203 (decomp.)
5	**2d**	CH_2Cl_2, rt	720	**4a**	17	193–195
6	**2e**	Benzene, reflux	180	**4b**[d]	75[e]	195–197 (decomp.)
7	**2f**	Benzene, rt	45	**4c**	25	141–142

[a] Compounds **3a–c**, **4a** and **4c** gave satisfactory elemental analyses and were characterized by IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopy. [b] Yields are of purified products, if not otherwise stated. [c] Uncorrected. [d] **4b** was purified by trituration with boiling light petroleum and did not give satisfactory elemental analyses. IR and mass spectra were taken and agreed with the structure. The structure of **4b** was confirmed by the preparation of the derivative **6** which gave satisfactory elemental analysis and was characterized by a complete set of spectra. [e] Yield of crude product.

noteworthy that methyl (5-methoxyindol-3-yl)cyanoacetate has been successfully transformed into tryptamine analogues, which have proved to be potential antihypertensive drugs.[9]

Extension of this work to the chlorosquarylation of benzofurans and benzothiophenes is under investigation.

Experimental

3-Chloro-4-(1,2-dimethyl-1*H*-indol-3-yl)cyclobut-3-ene-1,2-dione 3a (Table 1, Entry 1)

To a stirred solution of squaric dichloride 1 (1.74 g, 12.0 mmol) in benzene (30 cm^3) was added a solution of 1,2-dimethylindole **2a** (2.00 g, 13.3 mmol) in benzene (30 cm^3) over 10 min. When the addition was completed, the mixture was stirred for a further 45 min at room temperature. The reaction mixture was then filtered and the filtrate evaporated to dryness, leaving a dark green solid. This solid was recrystallized twice from $CHCl_3$–light petroleum (the first time with the aid of charcoal) to give **3a** as greenish crystals (1.83 g, 51%), mp 163–164 °C (decomp.) (Found: C, 64.4; H, 4.0; Cl, 13.6; N, 5.4. $C_{14}H_{10}ClNO_2$ requires C, 64.75; H, 3.88; Cl, 13.65; N, 5.39%); ν_{max}(KBr)/cm^{-1} 3020, 2920, 1780, 1750, 1600, 1535, 1490, 1440, 1400, 1100, 840 and 745; δ_H(400 MHz; $CDCl_3$) 2.78 (3 H, s), 3.74 (3 H, s), 7.24–7.32 (3 H, m) and 8.02 (1 H, d, J 7.8 Hz); δ_C(100.6 MHz; $CDCl_3$) 13.7, 30,4, 104.0, 110.0, 122.2, 122.9, 123.6, 125.5, 138.4, 146.3, 171.7, 187.5, 190.5 and 194.7; m/z (EI) 261 (M^+, 11%), 259 (M^+, 34), 205 ($M^+ - 2CO$, 34) and ($M^+ - 2CO$, 100).

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