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THE CHEMISTRY OF VICINAL TRICARBONYLS. FORMATION OF CARBAZOLE DERIVATIVES.

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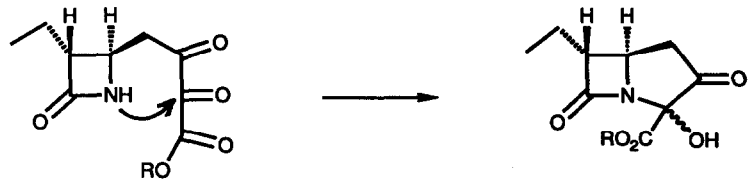
Summary: The indole tricarbonyl derivative **1** reacts with Schiff bases **2a-c** to form substituted carbazoles **3a-c**.

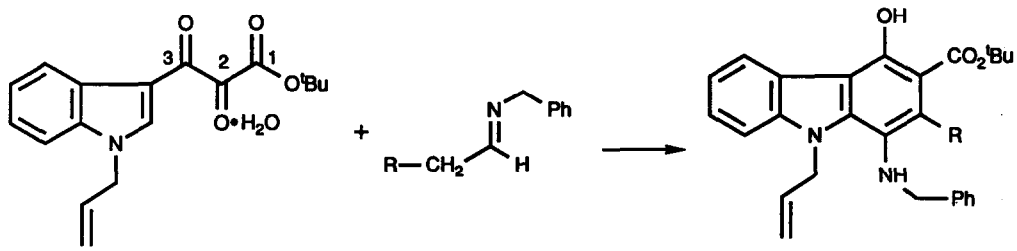
In earlier work, we showed that the C-2 carbonyl group in a 1,2,3-tricarbonyl system is a powerful center of electrophilic reactivity for intramolecular nucleophilic reaction, as in the formation of the carbapenam system from a β-lactam precursor (equation 1).[1] Our studies have also provided other examples of related intra- and intermolecular nucleophilic reactions in syntheses of prodigiosin,[2] and alkaloids in the vincamine,[3] erythrina,[4] and isoquinoline[5] series.



(eq. 1)

We now report that treatment of the indole tricarbonyl system **1** with aldehyde imines **2a-c** leads directly to carbazole derivatives **3a-c** by a process involving addition, cyclization and dehydration (Scheme 1). Methods

Scheme 1



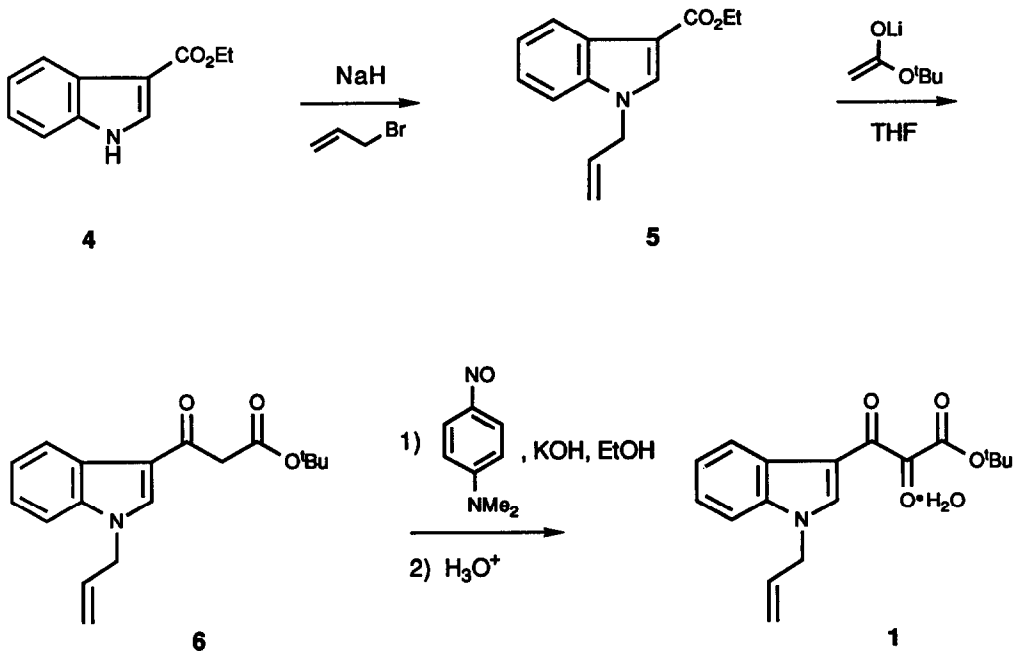
1 **2a-c**

3a, R = $(CH_3)_2CH$ (63%)
b, R = $CH_3(CH_2)_2$ (53%)
c, R = $CH_3(CH_2)_3$ (41%)

for the formation of substituted carbazoles are of special interest in connection with the recent isolation of several highly substituted carbazoles showing antimicrobial[6a] and antiviral[6b] activity.

The tricarbonyl reagent chosen for this study was the *N*-allyl indole derivative **1**, prepared as shown in Scheme 2.[7] Ethyl indole-3-carboxylate **4** was *N*-alkylated using NaH and allyl bromide (97%). The resulting compound **5** was then allowed to react with the anion of *t*-butyl acetate to form **6** (72%). This β-keto ester could be converted to the tricarbonyl derivative **1** (m. p. 95-96°C)[8] by Sachs' procedure employing the base-catalyzed condensation of *p*-nitrosodimethylaniline,[9,10] followed by acid hydrolysis (51%).

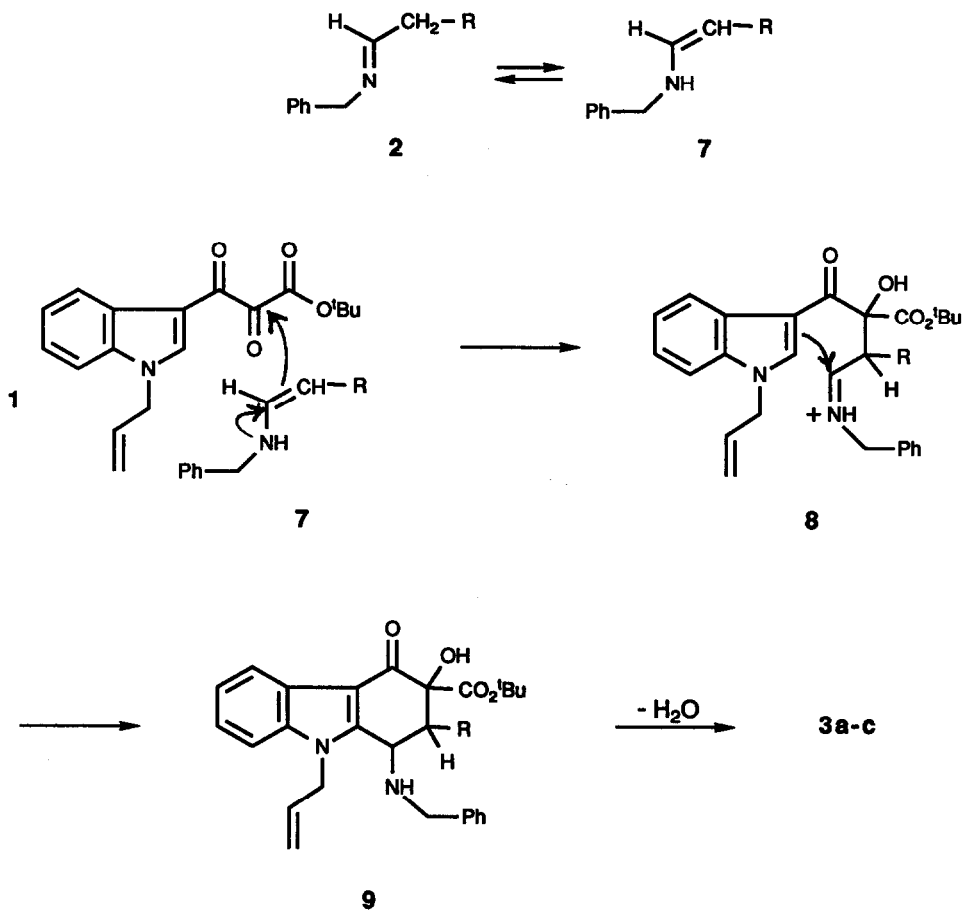
Scheme 2



When the indole **1** was warmed to 50°-60°C with an excess of the Schiff bases (**2a-c**),[11] facile transformation to *N*-benzylamino-4-hydroxy carbazole carboxylates (**3a-c**) took place (Scheme 1).[12] The products could be isolated in yields of 41-63% after chromatography.[13] The reaction appears to be general for aldehyde imines of structure R-CH_2-CH=N-R^1 although the Schiff bases of aldehydes having low molecular weight such as acetaldehyde or propionaldehyde tend to decompose too rapidly for effective use in the cyclization. Thus far, we have studied only cases where R^1 = CH_2Ph.

We picture the transformation of **1** to **3a-c** according to the sequence outlined in Scheme 3. Tautomerization of the imine **2** to the enamine **7** provides the donor species which initiates the addition leading to **8**. Intramolecular cyclization to **9** is then followed by dehydration and aromatization to **3**.

Scheme 3



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8 Spectroscopic data for **1**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.48-8.39 (m, 1 H), 8.30 (s, 1 H), 7.45-7.31(m, 3 H), 6.13-5.91 (m, 1 H), 5.85-5.46 (br s, 2 H, H_2O), 5.39-5.11 (m, 2 H), 4.82 (d, 2 H, J = 5 Hz), 1.64 (s, 9 H). IR ($CHCl_3$) 3050, 1750, 1660, 1540, 1250 cm^{-1}. MS (EI) 313, 184, 57. HRMS Calcd. for $C_{18}H_{19}NO_4$: 313.1315; Found : 313.1300.

9 Sachs, F.; Rohmer, A. *Ber.* **1902**, *35*, 3307.

10 For a review of the preparation and reactions of vicinal tricarbonyls see: Rubin, M. B. *Chem. Rev.* **1975**, *75*, 177.

11 The following is a general procedure for preparing the Schiff bases: The aldehyde (1mmol) was added dropwise to a solution of benzylamine (1mmol) in methylene chloride (5 ml) at room temperature. After anhydrous $MgSO_4$ (1g) was added, the reaction mixture was stirred at room temperature for 4 h. The reaction mixture was then filtered and concentrated under reduced pressure. The imine thus isolated was used immediately for the cyclization.

12 For a typical run, two equivalents of the desired Schiff base was added to a solution of the tricarbonyl derivative in benzene (0.05 M) at room temperature under an atmosphere of nitrogen. The resulting solution was heated at 50°-60°C and the reaction monitored by TLC. When all of the tricarbonyl was consumed, the reaction mixture was cooled to room temperature and the solvent removed under reduced pressure. The crude product was then purified by flash chromatography.

13 All new compounds were characterized by ^{1}H NMR, IR, MS, and high resolution MS. Spectroscopic data for **3a** (m. p. 78-79°C) : ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.65-7.59 (d, 1 H, J = 5 Hz), 7.52-7.33 (m, 6H), 7.25-7.13 (m, 2 H), 6.23-6.18 (m, 1 H), 5.42-5.19 (m, 2 H), 4.85 (d, 2 H, J = 5 Hz), 4.51, (d, 1 H, J = 12 Hz), 4.29 (d, 1 H, J = 12 Hz), 2.96-2.81 (m, 1 H), 1.63 (s, 9 H), 1.25 (app. t, 6 H, J = 7 Hz). IR ($CHCl_3$) 3050, 1745, 1675, 1580, 1160 cm^{-1}. MS (EI) 470, 369, 279. HRMS Calcd. for $C_{30}H_{34}N_2O_3$: 470.2571; Found 470.2560.

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