Dipolar Cycloaddition Reactions of Isatin Derived Azomethine Ylide with 3,4-Diphenylcyclobutene-1,2-dione: Synthesis of Novel Spiro[oxindole-3,2'-pyrrolidine] Derivatives

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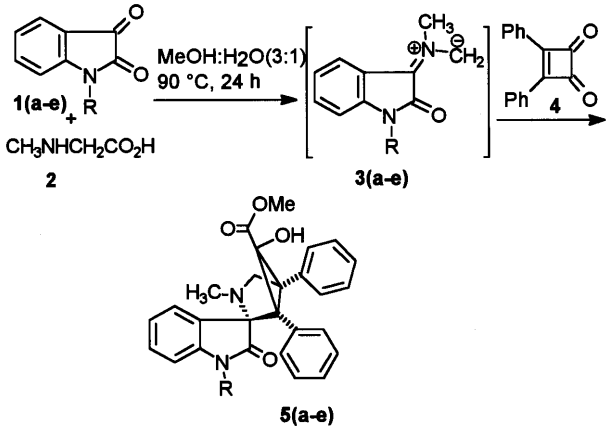
Azomethine ylide, generated by the decarboxylative condensation of sarcosine with isatins has been trapped by 3,4-diphenylcyclobutene-1,2-dione to afford novel spiro[oxindole-3,2'-pyrrolidine] derivatives.

The cycloadditions of dipolar species to *o*-quinones have attracted our attention considerably.[1–4] In this context, it was of interest to probe the reactivity of azomethine ylides[5] to *o*-quinones and other 1,2-dicarbonyl compounds. In view of its potential application in the construction of complex spirooxindole derivatives and the recent work by Grigg[6] and others,[7] the azomethine ylide derived from isatin and sarcosine appeared particularly attractive for our investigations.

Our studies were initiated with the reaction of azomethine ylide **3a** generated by the decarboxylative condensation of sarcosine **2** with 1-methylisatin[8] **1a** and 3,5-di-*tert*-butyl-1,2-benzoquinone. This reaction did not lead to any cycloadduct; only the catechol resulting from the reduction of the quinone was isolated. It was then decided to explore the reaction with other 1,2-dicarbonyl compounds such as cyclobutenediones. It may be noted that although the chemistry of the latter has been extensively studied,[9] their dipolar cycloaddition reactions have not received much attention. The scant information available in the literature is concerned with the reactions involving diazomethane[10] and nitrile oxides.[11]

It was found that 3,4-diphenylcyclobutene-1,2-dione **4** on reaction with azomethine ylide **3a**, in MeOH:H_2O system at 90 °C proceeded smoothly to afford a colorless crystalline product **5a, (**Scheme 1**)** in 58% yield[12] (Table 1, Entry 1). Analogous



Scheme 1.

Table 1. Dipolar cycloaddition reactions of azomethine ylide with cyclobutenedione

Entry	1	R	5	Yield a (b)/%	Mp/ °C
1	**1a**	Me	**5a**	58 (69)	238-240
2	**1b**	Ph	**5b**	48 (65)	174-176
3	**1c**	Bn	**5c**	38 (53)	164-166
4	**1d**	H	**5d**	49 (57)	106-108
5	**1e**	H, 5-Br	**5e**	31 (43)	233-235

[a]Isolated yield after column chromatography. [b]Based on recovered dione **4.**

reactivity was observed with other substituted isatins and the results are summarized in Table 1.

The products were purified by silica gel column chromatography and characterized by spectral analysis. Ultimately the structure was confirmed unequivocally by single crystal X-ray analysis of **5a** (Figure 1).

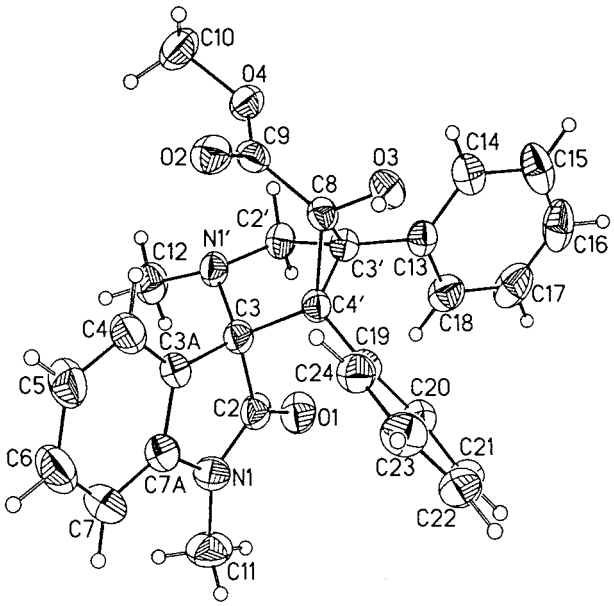


Figure 1. X-Ray crystal structure of **5a.**

A mechanistic rationalization for the formation of **5a** as outlined in Scheme 2 may be invoked. It is reasonable to assume that the cycloaddition proceeds by the initial attack of azomethine ylide **3a** preferentially on the carbon–carbon double bond of 3,4-diphenylcyclobutene-1,2-dione leading to a cyclobutane derivative which then undergoes rearrangement.[13]

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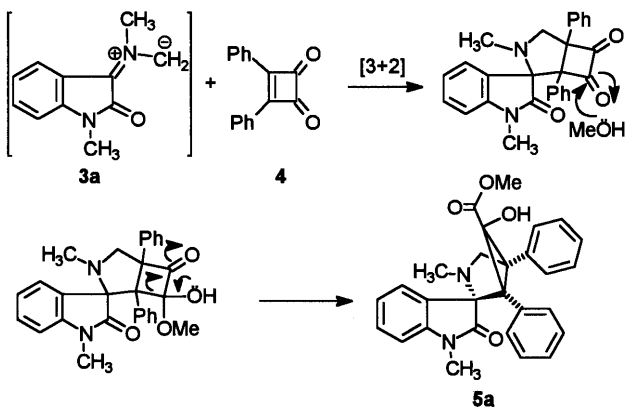

Scheme 2.

The observed chemoselectivity in these cycloadditions[14] can be easily understood in terms of Frontier Molecular Orbital theory, which is suggestive of a type 1 FMO interaction.[15]

The typical experimental procedure of the multicomponent reaction is as follows: To a solution of 1-methylisatin **1a** (0.206 g, 1.28 mmol) in methanol (6 mL) was added sarcosine **2** (0.228 g, 2.56 mmol) in distilled water (2 mL) and the mixture stirred at 90 °C for 5 min. This was followed by the addition of 3,4-diphenylcyclobutene-1,2-dione **4** (0.200 g, 0.85 mmol). The reaction mixture was stirred at 90 °C for 24 h. It was then processed by the usual aqueous work up and purified by silica gel column chromatography. The unreacted cyclobutenedione **4** (0.031 g) was eluted using hexane–ethyl acetate (95:5) mixture. The cycloadduct **5a**, was separated using 10% ethyl acetate in hexane as eluent (0.226 g, 58%) as colorless crystals. Yield based on recovered cyclobutenedione was 69%. The reaction is extremely sluggish in aqueous acetonitrile.

In conclusion, it is found that 3,4-diphenylcyclobutene-1,2-dione undergoes facile dipolar cycloaddition with azomethine ylide, generated from isatins, yielding novel spiro[oxindole-3,2'-pyrrolidine] derivatives. It is worthy of note that the spiro[oxindole-3,2'-pyrrolidine]ring system is a recurring structural motif in a number of natural products with remarkable biological activity.

From our preliminary studies, it appears that the reaction is general for azomethine ylide derived from a variety of 1,2-diones. The results of our detailed investigations will be reported in due course.

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