



Silica Gel-Supported Hetero Diels-Alder Reactions of Quinolinetriones.

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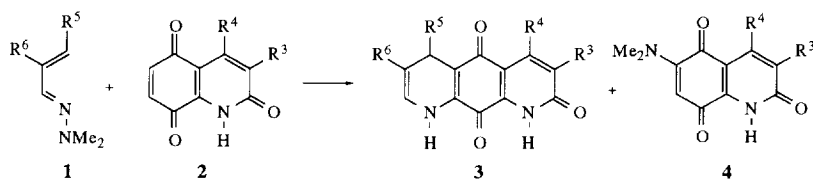
Abstract: When 2,5,8(1*H*)-quinolinetriones were supported on silica gel and treated with 1-dimethylamino-1-azadienes in excess, followed by rapid chromatography, the corresponding 5,8-dihydro-1,8-diazaanthracene-2,9,10-triones or 1,8-diazaanthracene-2,9,10-triones were obtained, normally in excellent yields. This procedure minimizes or completely prevents the addition of dimethylamine to the starting quinone, a problem that has seriously limited in the past the usefulness of 1-dimethylamino-1-azadienes as heterodienes for quinones. Copyright © 1996 Published by Elsevier Science Ltd

Diels-Alder reactions of 1-azadienes¹⁻³ are very important synthetic transformations and have found use in the preparation of compounds containing pyridine, quinoline, mono- and diazaanthracene and other nitrogen rings. In particular, α,β -unsaturated dimethylhydrazones have been widely used in hetero Diels-Alder reactions⁴ with electron-deficient partners as key steps in a variety of syntheses of natural products and other biologically relevant heterocycles.⁵ Due to our interest in the synthesis of antitumour⁶ 1,8-diazaanthracene-2,9,10-triones and 1,8-diazaanthracene-2,8,9,10-tetraones related to the antibiotic Diazaquinomycin A,⁷ we have examined⁸ the reactions between a number of 1-dimethylamino-1-azadienes (**1**) and 2,5,8-quinolinetriones (**2**), finding that in many cases the yield of the desired cycloaddition is moderate or low due to the competitive formation of secondary products derived from reaction of dimethylamine with the starting quinone or the final product. Other workers have noticed similar problems in related reactions using quinones as dienophiles,⁹ and a variety of experimental devices have been proposed for preventing this side reaction. For instance, the use of a stream of inert gas to remove dimethylamine from the reaction medium prior to its addition to the quinone may be useful, but it normally fails to completely solve the problem, particularly in the case of rapid reactions. Replacement of the dimethylamino group of the diene by other electron donors that do not liberate nucleophilic species has also been attempted, and 1-acylamino-1-azadienes¹⁰ have been proposed with this aim.^{8b} However, they are much less reactive than dimethylhydrazones and their Diels-Alder reactions require harsh reaction conditions, even with very reactive quinones. In a different approach, trapping the dimethylamine by addition of acid might prevent its addition to the unreacted starting quinone. However, according to the literature, the presence of Lewis¹¹ or Brønsted¹² acids in reaction media containing 1-dimethylamino-1-azadienes and simple quinones results in the isolation of furoquinoline derivatives from Michael addition to the quinone system followed by 5-*exo-trig* ring

closure, in an overall [3 + 2] cycloaddition. These compounds are also formed when the dienes or the dienophiles are very polarized due to electronic effects.^{6c,8c,13}

In the search for an alternative procedure, we envisaged that silica gel might provide a useful alternative to previously assayed additives, since we hoped that its acidic character would be sufficient to retain the dimethylamine but too weak to trigger the competing [3 + 2] cycloaddition. Unfortunately, simple addition of silica gel to the reacting mixture gave results only marginally better than under the standard conditions. However, when the quinones **2**¹⁴ were supported on silica gel prior to the addition of the heterodienes **1**¹⁵ a considerable improvement was observed, particularly when the Diels-Alder reaction was immediately followed by chromatographic separation of the reaction products. Under those conditions, secondary products **4** were minimized and the isolated yields of cycloadducts rose to 80-90 % levels in most cases. As expected,^{8b,c} use of heterodienes or quinones bearing substituents at their respective C-4 positions led to 5,8-dihydro-1,8-diazaanthracene-2,9,10-triones **3**, from cycloaddition followed by elimination of dimethylamine and isomerization. On the other hand, when either the diene or the dienophile lacked a substituent in that position, compounds **3** were not stable and were oxidized *in situ* to the aromatic derivatives **5**.¹⁶ The results obtained in the reactions of several α,β -unsaturated dimethylhydrazones **1** and several 2,5,8(1*H*)-quinolinetriones **2** are summarized in Tables 1 and 2.

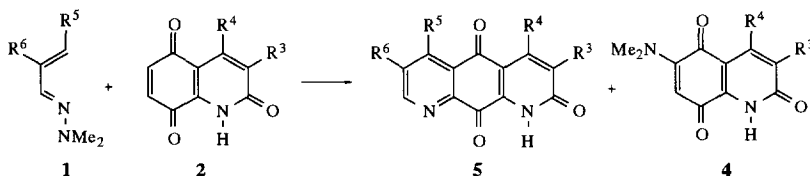
Table 1.- Yields of Hetero Diels-Alder Reactions Leading to 5,8-Dihydro-1,8-Diazaanthracene-2,9,10-triones



R ³	R ⁴	R ⁵	R ⁶	Standard conditions		SiO ₂ support	
				% 3	% 4	% 3	% 4
H	CH ₃	CH ₃	H	51	35 ^a	88	0
H	CH ₃	C ₂ H ₅	CH ₃	47	45 ^a	78	10
CH ₃	CH ₃	CH ₃	H	32	42 ^b	70	6
H	C ₂ H ₅	CH ₃	H	29	59 ^b	84	0
H	C ₃ H ₇	CH ₃	H	32	50 ^b	92	0

^a Data obtained from reference 8b. ^b Data obtained from reference 14c.

Table 2.- Yields of Hetero Diels-Alder Reactions Leading to 1,8-Diazaanthracene-2,9,10-triones



R ³	R ⁴	R ⁵	R ⁶	Standard conditions		SiO ₂ support	
				% 5	% 4	% 5	% 4
H	CH ₃	H	CH ₃	48	20 ^a	88	0
H	CH ₃	H	C ₂ H ₅	42	33 ^b	89	0
H	(CH ₂) ₂ C ₆ H ₅	H	CH ₃	49	15 ^c	82	0
C ₆ H ₅	H	CH ₃	H	40	20 ^d	57	7

^a Data obtained from reference 8a. ^b Data obtained from reference 8b. ^c Data obtained from reference 14c.

^d Data obtained from reference 8c.

Representative procedure: Silica gel (125 mg) was added to a solution of 4-methyl-2,5,8(1H)-quinolinetrione^{14a} (25 mg, 0.13 mmol) in chloroform (10 ml). The suspension was stirred at room temperature for 15 min and evaporated to dryness. The silica gel-supported quinone was placed on top of a chromatography column containing silica gel (6 g) and was covered with a layer of sand. Neat crotonaldehyde dimethylhydrazone (150 mg, 10 eq) was added and covered with a second layer of sand. The diene was allowed to permeate the sand and contact the silica gel layer over 1 min. The column was then eluted with a gradient from dichloromethane to 1:1 dichloromethane-ethyl acetate, to yield recovered azadiene and 29 mg (88 %) of 4,5-dimethyl-5,8-dihydro-1,8-diazaanthracenetrione^{8b} as a green solid.

In conclusion, we present a very simple experimental modification that leads to a considerable improvement of hetero Diels-Alder reactions between 1-dimethylamino-1-azadienes and 2,5,8(1H)-quinolinetriones.

ACKNOWLEDGEMENTS

Financial support from CICYT (projects FAR 553-90 and PTR 0028-93), Comunidad Autónoma de Madrid (research studentship to P. L.-A.) and Universidad Complutense (research studentship to M. A. A.) is gratefully acknowledged.

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14. For the preparation of the 2,5,8(1*H*)-quinolinetriones employed, see: a) 4-methyl derivative: Avendaño, C.; de la Cuesta, E.; Gesto, C. *Synthesis* **1991**, 727; b) 3-phenyl derivative: Alonso, M. A.; Blanco, M. M.; Avendaño, C.; Menéndez, J. C. *Heterocycles* **1993**, *36*, 2315; c) other derivatives: López-Alvarado, P. Ph. D. Thesis. Universidad Complutense, Madrid, 1995.
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16. The mildness of the modified conditions described herein allowed to isolate for the first time a 3,5-disubstituted-5,8-dihydro-1,8-diazaanthracene-2,5,8-trione (compound **3**, R³ = C₆H₅, R⁵ = CH₃, R⁴ = R⁶ = H), but it was quantitatively oxidized to the corresponding aromatic derivative **5** upon a second column chromatography or upon standing for 12 h in an NMR tube in pyridine-d₅ solution at 4 °C.

(Received in UK 23 July 1996; accepted 1 August 1996)