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CYCLOADDITION REACTION OF PYRIMIDINE-DIENOLS WITH DIENOPHILES. A NEW APPROACH TO QUINAZOLINES

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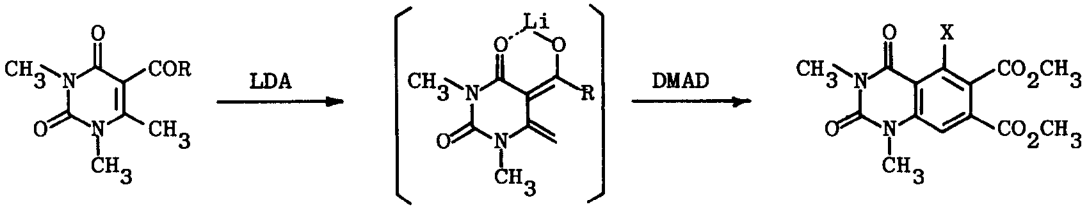
Summary A new synthetic approach to quinazolines bearing a carboxy group is described. Reaction of 5-carbonyl substituted 1,3,6-trimethyluracils (I) with dimethyl acetylenedicarboxylate or electron-deficient olefines affords quinazoline derivatives (III-VI) via pyrimidine(Z)-dienols (II) formed by base-catalyzed isomerization.

It has been shown[1)] that ortho-alkyl substituted aromatic carbonyl compounds, e.g. o-methylbenzaldehyde, o-benzylbenzaldehyde and 2-methylbenzophenone, undergo photochemical enolization to give a dienol which is trapped in the Diels-Alder reaction. We have found that the pyrimidine-dienols, derived from 5-carbonyl substituted 1,3,6-trimethyluracils (I) by base catalyzed enolization, react with electrone-deficient dienophiles to afford quinazolines with regio- and stereoselectivity.

A solution of 5-formyl-1,3,6-trimethyluracil (Ia) (2.75 mmol) in tetrahydrofuran (THF) was stirred with lithium diisopropylamide (LDA) (4.13 mmol) at -70°C and followed by addition of dimethyl acetylenedicarboxylate (DMAD) (4.13 mmol). The solution was evaporated and neutralized to give the dimethyl quinazoline-6,7-dicarboxylate (IIIa)[2)] in 83% yield. Similar treatment of 5-acetyl-(Ib) and 5-ethoxycarbonyl-1,3,6-trimethyluracil (Ic) with DMAD gave the corresponding quinazolines IIIb (49%) and IIIc (56%) with elimination of water or ethanol.

We have also investigated the reaction of I with a variety of electron-deficient olefines such as dimethyl maleate, dimethyl fumarate, and methyl vinyl ketone. The cycloadducts obtained are summarized in Table. Dimethyl maleate and dimethyl fumarate reacted with I to give 1:1 adducts (IV and V), respectively, which have the same composition but differ in stereochemistry. In the NMR

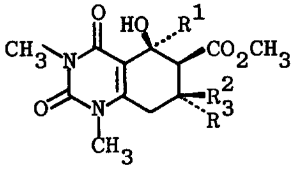
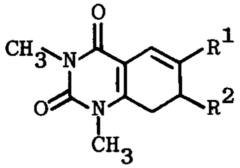


Ia: R=H
Ib: R=CH_3
Ic: R=OC_2H_5

II

IIIa: X=H mp 192-193
IIIb: X=CH_3 mp 156-157
IIIc: X=OH mp 203-204

Table Formation of Quinazolines (IV-VII)

structure	compd.	R^1	R^2	R^3	mp °C	yield %
	IVa	H	CO_2CH_3	H	185-187	56
	IVb	CH_3	CO_2CH_3	H	193-195	63
	Va	H	H	CO_2CH_3	198-200	70
	Vb	CH_3	H	CO_2CH_3	215-218	47
	VI	CO_2CH_3	H		202-203	36
	VII	CO_2CH_3	CO_2CH_3		190-191	

spectra of IVa and Va, the signal of each C-5 proton was observed as doublet at δ 5.19 and δ 4.93 with the same coupling constant (4Hz). Compound IVa was converted to the 7,8-dihydroquinazoline (VII) by stirring with thionyl chloride in benzene at room temperature (80%) or heating with p-toluenesulfonyl chloride in pyridine at 80°C (55%). Similar treatments of Va afforded the same product (VII) in 59% and 60% yields, respectively. From these results, it might be concluded that the respective configurations of IVa and Va are all-cis and cis-trans as depicted in Table.

The overall mechanism of the cycloaddition reaction can therefore be interpreted as follows : abstraction of the proton from the C-6 methyl group of I in basic medium would afford the (Z)-dienol (II) which is stabilized in preference to the (E)-dienol by intramolecular interaction between the hydroxy and C-4 carbonyl groups, followed by the Diels-Alder reaction of II with dienophiles via an endo-approach[3] to give the cycloadducts (IV, V) with high stereoselectivity.

Regioselectivity, as well as stereoselectivity, was observed in the cycloaddition reaction of Ia with methyl vinyl ketone. The major product obtained was not the 7-acetyl- but the 6-acetylquinazoline (VI) formed by dehydration of the adduct.

References and Notes

1) P. G. Sammes, Tetrahedron, 32, 405 (1976); M. Pfau, J. E. Rowe, Jr., and N. D. Heindel, ibid., 34, 3469 (1978) and references therein.
2) All new compounds reported herein gave satisfactory elemental analysis and spectral data.
3) Similar selectivity has been observed in the reaction between the photodienol and maleic anhydride; F. Nerdel and W. Brodowski, Chem. Ber., 101, 1398 (1968).

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