REACTION OF CONJUGATED ENAMINES WITH DIAZONIUM SALTS[1]. A convenient Synthesis of Cinnoline Derivatives.

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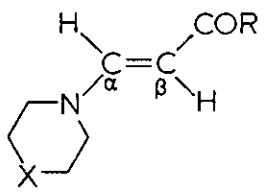
Aryldiazonium salts react with enamine esters and enamine amides to give iminium hydrazones, which cyclize with subsequent deamination to yield cinnoline derivatives.

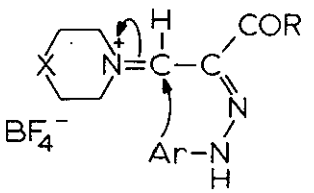
Reaction of enamines with diazonium salts is of considerable synthetic interest, particularly since the primary product of the electrophilic attack upon the enamine system can undergo diverse types of transformations depending upon the conditions of the reaction[3]. It has been recently shown in this laboratory that enamine esters react with aryldiazonium salts to give hydrazones which, upon treatment with base, result in cyclization to imidazoazacycloalkane derivatives[1]. We now wish to report the conversion of the same hydrazone intermediate to cinnoline derivatives. The sequence of transformations, which can be carried out in "one pot" without isolation of the intermediate, constitutes a facile approach to compounds incorporating the cinnoline moiety.

The enamine esters 1a-c and the enamine amides 1d-f were conveniently accessible via the addition of the appropriate seconda-



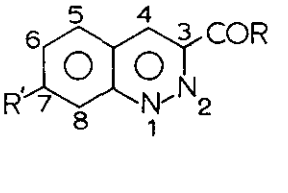
1

	X	R
a.	—	OEt
b.	O	OEt
c.	CH_2	OEt
d.	—	$N\langle(CH_2)_4$
e.	O	$N\langle(CH_2)_4$
f.	CH_2	$N\langle(CH_2)_4$



2

	X	Ar	R
a.	—	Ph	OEt
b.	O	Ph	OEt
c.	CH_2	Ph	OEt
d.	—	(m)MeOPh	OEt
e.	O	Ph	$N\langle(CH_2)_4$
f.	CH_2	Ph	$N\langle(CH_2)_4$



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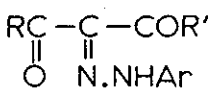
	R	R'
a.	OEt	H
b.	OEt	OMe
c.	$N\langle(CH_2)_4$	H
d.	$N\langle(CH_2)_4$	OMe



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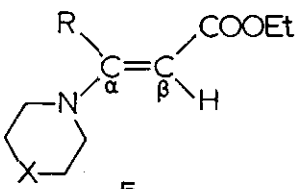
	R	R'
a.	H	$N\langle(CH_2)_4$
b.	Me	OEt
c.	Ph	OEt



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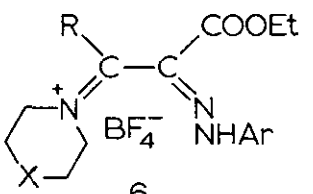
	X	R
a.	—	Me
b.	O	Me
c.	O	Ph



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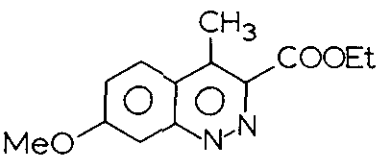

7

ry amine to ethyl propiolate or to the pyrrolidine amide of propiolic acid[4], respectively.

When benzenediazonium fluoroborate was allowed to react with 1a-c (CH_3CN, 30 min.R.T.), the corresponding iminium salts were isolated in excellent yields (~90%). Attempts to isolate the corresponding iminium salts from the reaction of 1e,f with the diazonium salt, led to the isolation of the hydrolytic product of 2e,f, namely 4a(Ar=Ph). When the reaction mixtures of 1b, 1e and 1f and benzenediazonium fluoroborate were refluxed in acetonitrile, the cinnoline derivatives 3a and 3c could be isolated as crystalline products, after column chromatography (silica gel). The mechanism of formation of 3a and 3c clearly involves intermediates of type 2 (R=OEt, $N<(CH_2)_4$), which cyclize via a nucleophilic attack of the aromatic moiety upon the iminium carbon; subsequent aromatization by loss of the amine leads to the cinnoline nucleus. Factors affecting the cyclization step will obviously influence the course of the reaction. In this connection it is significant, that while salts 2a and 2c do not cyclize upon heating in acetonitrile, the corresponding m-methoxybenzene derivative 2d smoothly cyclizes to the cinnoline ester 3b. The methoxy substituent clearly operates by enhancing the nucleophilic character of the aromatic moiety in the ring-closure reaction. Consistent with this argument is the observation that the enamine derivatives 1b-f all react with m-methoxybenzenediazonium fluoroborate (CH_3CN, room temperature) to yield the corresponding cinnolines 3b and 3d, in good yield. Under the latter conditions 1a gives the iminium salt 2d as the sole product of the reaction.

Physical Characteristics and Yields of Iminium Salts 2a-d and Cinnolines 3a-d.

TABLE

Product	m.p.	δ $\underline{CH}=N^+$	δ $C_4-\underline{H}$	Yield %
2a	126-127°	8.80 br.s		∿ 90
2b	159-162°	8.94 br.s		∿ 90
2c	113-115°	8.69 br.s		∿ 90
2d	141-143°	9.09 br.s		86
3a	88-91°		8.66 s	53
3b	121-126°		8.48 s	63
3e	108-110°		8.56 s	71
3d	177-178°		8.42 s	61
7	156-159°			57

The aforementioned results reveal two structural factors in the enamine derivative, which appear to affect the cyclization process. The sluggishness of 2d towards cyclization (in comparison with similar salts formed in the reaction of 1b and 1c with (m)MeO-$C_6H_4N_2^+$ BF_4^-) and the non-reactivity of 2a and 2c point to the role of both the basicity and the ring-size[5] of the base-component of the enamine. While high basicity of piperidine and pyrrolidine will make the corresponding iminium salts less reactive in the cyclization reaction (in comparison with the morpholinium salts), the known stability of the double bond in an exocyclic configuration to the five ring[6], accounts for the further decrease in the reactivity of the pyrrolidinium salts 2a and 2d. A comparison of the behaviour of the enamine ester (1c) with that of the enamine amide (1f) shows that the latter reacts with benzenediazonium fluoroborate to form the

cinnoline system under conditions where the former is inactive. In fact, the iminium salt derived from 1c (viz. 2c) is unaffected in refluxing acetonitrile. This difference may be attributed to the fact that the ester function withdraws electrons more strongly from the arylhydrazone moiety than the amide group[7], whereby the nucleophilic character of the aryl group is suppressed. To study the overall role of the effect of C_α-substitution in the enamine esters, the reaction of 5a-c with m-methoxybenzenediazonium fluoroborate was examined. At room temperature (CH_3CN) the formation of the salts corresponding to 6 could be evidenced by isolation of their hydrolytic products (4b, Ar = (m)MeOPh, 4c, Ar = (m)MeOPh). When the reaction mixtures containing the aforementioned iminium salts were heated to reflux in acetonitrile, only in the case of the salt derived from 5b, cyclization to the cinnoline ester 7 (57%) was observed. While the difference in the reactivities of the pyrrolidine and the morpholine enamines (5a and 5b) is again observable, it is noteworthy that the phenyl substituent at C_α hinders the cyclization step. A possible explanation of the latter result may lie in the deactivation of the iminium carbon (towards nucleophilic attack) by electron release from the phenyl group.

Correct microanalytical and/or spectral data have been obtained for all compounds described in this communication.

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