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HETEROCYCLIZATION OF FUNCTIONALIZED KETENE ACETALS: SYNTHESIS OF PYRIMIDINES VIA VINYLAMIDINE INTERMEDIATES

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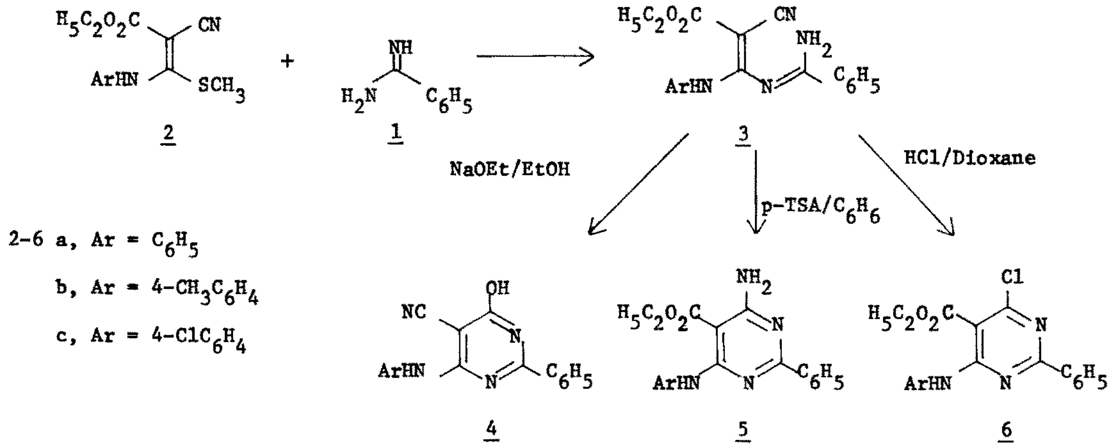
Summary: Stable N-(carbethoxycyanovinyl)amidines have been isolated from the reaction of benzamidine with carbethoxycyanoketene S,N-acetals and have been found to cyclize to 4-chloro-, 4-amino- and 4-hydroxypyrimidines depending upon the cyclizing agent employed.

The pyrimidine syntheses from amidines and 1,3-dicarbonyl compounds have generally been assumed to proceed via non-isolable vinylamidine intermediates. There are only a few reports on the successful isolation of functionalized vinylamidine intermediates, as for example, in the reaction of ethyl ethoxymethylenecyanoacetate with certain amidines[1-3]. We have observed that while the condensation of benzamidine 1 with ketene S,N-acetals 2a-c in the presence of sodium ethoxide in ethanol, at reflux, yields 4-hydroxy-5-cyano-2-phenylpyrimidines 4a-c, the reaction of benzamidine 1 with 2a-c, at ambient temperature, gives stable N-(cyanovinyl)amidines 3a-c as the isolable product of the reaction, in good yields.

Furthermore, the cyclization of these vinylamidines 3a-c to pyrimidines can be directed by the choice of the experimental conditions. While sodium ethoxide in ethanol transforms vinylamidines 3a-c to 4-hydroxy-5-cyanopyrimidines 4a-c, treatment with p-toluenesulfonic acid in benzene at reflux bring about their cyclization to 4-amino-5-carbethoxy-2-phenylpyrimidines 5a-c.



2-6 a, Ar = C_6H_5
b, Ar = $4\text{-}CH_3C_6H_4$
c, Ar = $4\text{-}ClC_6H_4$

Interestingly, the vinylamidines 3a-c, when treated with a stream of dry hydrogen chloride gas in dioxane, undergo an unusual mode of cyclization to yield, directly, the 4-chloro-5-carbethoxy-2-phenylpyrimidines 6a-c. This novel cyclization of cyanovinylamidines to 4-chloropyrimidines bears a formal resemblance to the reported[4] direct formation of condensed 4-chloropyrimidines in the hydrogen chloride catalyzed condensation of a nitrile with an o-aminonitrile, presumed to proceed through non-isolable o-cyanoamidine intermediates.

TABLE I

Physical constants of Ketene S,N-acetals 2a-c, Vinylamidines 3a-c and Pyrimidines 4a-c, 5a-c, and 6a-c

No.	Mol. Formula[a]	Mol. Wt.	sol. of crystn.[e]	M.P.°C	% Yield
2a	$C_{13}H_{14}N_2O_2S$	262	B-H	83-85[c]	85[b]
2b	$C_{14}H_{16}N_2O_2S$	376	B-H	79-81	81[b]
2c	$C_{13}H_{13}N_2O_2SCl$	296[d]	B-H	110-112	80[b]
3a	$C_{19}H_{18}N_4O_2$	334[d]	B	180-182	70
3b	$C_{20}H_{20}N_4O_2$	348	B	188-190	62
3c	$C_{19}H_{17}N_4O_2Cl$	368[d]	E	223-225	68
4a	$C_{17}H_{12}N_4O$	288[d]	D-E	> 360	65
4b	$C_{18}H_{14}N_4O$	302[d]	DM-E	> 360	68
4c	$C_{17}H_{11}N_4OCl$	322[d]	DM-E	> 360	70
5a	$C_{19}H_{18}N_4O_2$	334[d]	E	135-137	53
5b	$C_{20}H_{20}N_4O_2$	348[d]	E	160-162	55
5c	$C_{19}H_{17}N_4O_2Cl$	368.5	E	183-185	59
6a	$C_{19}H_{16}N_3O_2Cl$	353[d]	H	132-134	50
6b	$C_{20}H_{18}N_3O_2Cl$	367[d]	H	116-118	51
6c	$C_{19}H_{15}N_3O_2Cl_2$	388	H	127-129	54

a) All the compounds gave correct analysis b) prepared by the reaction of arylamines with ethyl (dimethylthiomethylene)cyanoacetate c) Reported M.P. 83°C Ref. No. 5 d) M^+ determined by mass spectra e) B = Benzene, D = Dimethylformamide, DM = Dimethyl sulfoxide, E = Ethanol, H = n-Hexane.

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