Tetrahedron Letters,Vol.24,No.30,pp 3051-3054,1983
Printed in Great Britain

0040-4039/83 $3.00 + .00

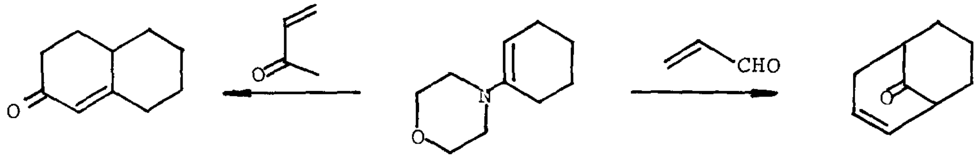
CYCLOAROMATIZATION REACTION OF ENAMINES

T.H. Chan and G.J. Kang

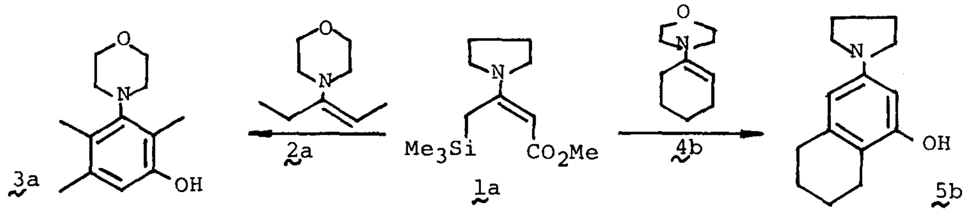
Department of Chemistry, McGill University, Montreal, Quebec, Canada H3A 2K6.

Abstract: Condensation of enamines with 4-trimethylsilyl-3-dialkylamino-crotonate esters under acid catalysed conditions gives aromatic compounds according to a 3C+3C or a 4C+2C manner depending on the structure of the enamine.

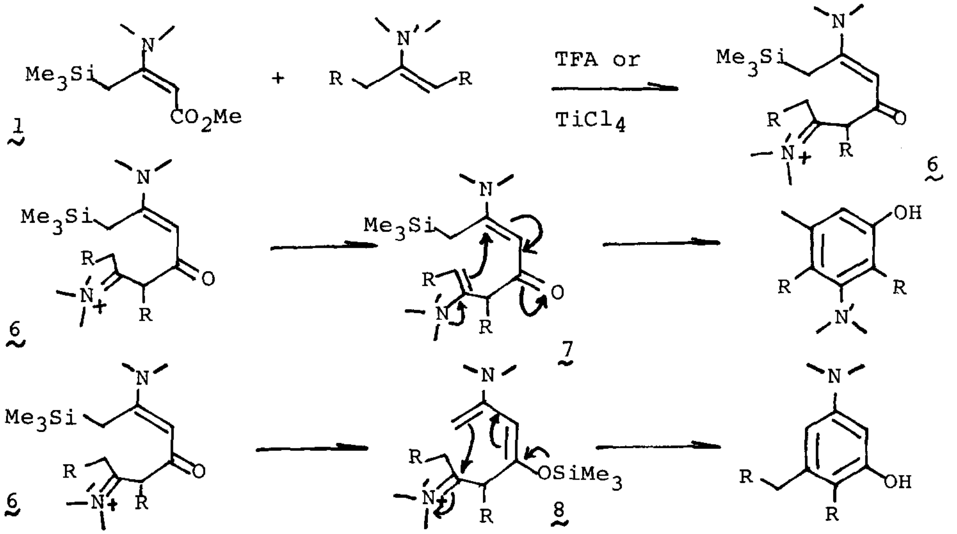
Annelation reactions involving enamines to give cyclohexenones are well-known[1]. They can be illustrated by the following examples[2,3]. A point of interest is that, depending on the nature of the other reactants, the same enamine can act as either a two-carbon (2C) or a three-carbon (3C) component in the annelation reaction.



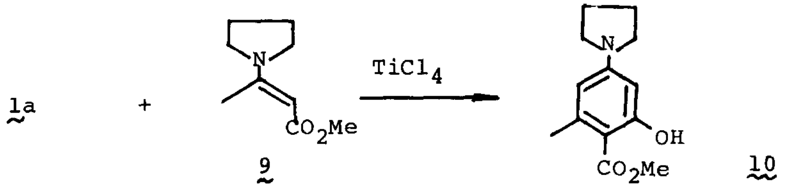
We wish to report here reactions of enamines which embody the following features: (a) the annelation is initiated by the reaction enamine with the ester carbonyl group of 4-trimethylsilyl-3-dialkylaminocrotonate esters (**1**)[4], (b) the reaction leads to the formation of highly substituted aromatic compounds and (c) with the same reactant **1**, different enamines react either as a 2C or as a 3C component depending on the structure of the enamines. The cycloaromatization reaction can be illustrated by the reaction of **1a** with 3-morpholinopentene (**2a**) to give the aromatic compound **3a** on the one hand, but with 1-morpholinocyclohexene (**4b**) to give **5b** on the other hand. Both reactions are conducted under acid-catalysed conditions with trifluoroacetic acid (TFA) or titanium tetrachloride ($TiCl_4$) as the acid.



It seems clear from the Table that enamines derived from acyclic ketones (2ab;11ab) give aromatic compounds by a 3C+3C annelation whereas enamines derived from cyclic ketones (4a-d) give aromatic compounds by a 4C+2C annelation with the enamine acting as the 2C component. A mechanism which is consistent with the above observation is presented in the following scheme:



The first step is condenation of the enamine with the carbonyl group of the ester 1 to give the intermediate 6. Isomerization of 6 to 7 followed by an intramolecular Michael condensation lead to aromatization in a 3C+3C combination. The silyl group is then protodesilylated under the reaction conditions[5]. For cyclic ketones (of 5-8 membered rings), the isomerization step does not lead to aromatization due to the strain in forming the final meta-cyclophanes. Isomerization of 6 to 8 by a 1,5-silyl shift intervenes[4]. Intramolecular Mannich reaction in a 4C+2C combination ensues giving the aromatic product. It follows from this mechanism that any structural feature which disfavors the isomerization of 6 → 7 will change the course of the reaction from a 3C+3C mode to the 4C+2C mode. This is indeed the case. When enamine 9 is used in the condensation with 1a, the aromatic compound 10 is formed in accordance with the 4C+2C combination.



The other corallary is that if the cyclic ketone (of the enamine) is of sufficiently large ring size so that the product m-cyclophane is structurally feasible[6], the 3C+3C cycloaromatization may reassert itself. This proves to be the case (2c,d)[8].

Finally, it remains to point out that the trimethylsilyl group in **1** plays a subtle but indespensible role in controlling the reaction. It discourages **1** from undergoing self-condensation[7]. It apparently activates the ester carbonyl in **1** so that it is preferentially attacked by enamine. It is also clear that the present study presents a way for the construction of highly substituted anilino compounds from acyclic precursors. Application of this approach to the synthesis of natural products will be explored in due course.

Acknowledgement: We thank NSERC of Canada and FCAC of Quebec for financial support. GJK thanks the government of the Peoples' Republic of China for the award of a scholarship.

References and Footnotes

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4. T.H. Chan and G.J. Kang, Tetrahedron Letters **23**, 3011 (1982).
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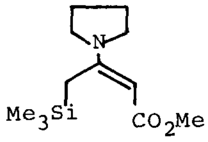
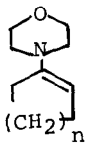
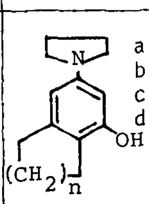
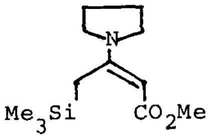
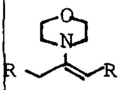
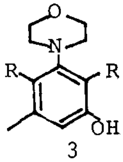
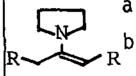
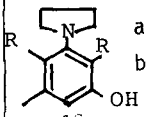
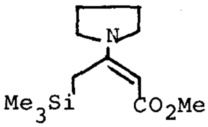
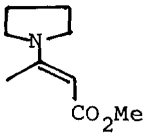
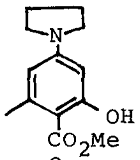
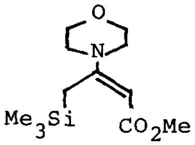
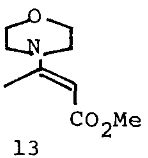
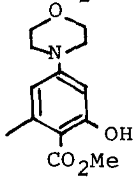
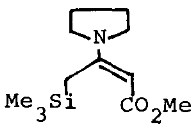
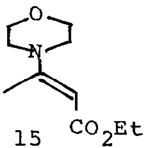
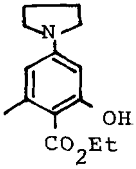
TABLE: Synthesis of aromatic compounds from the acid-catalysed condensation of enamine with 4-trimethylsilyl-3-dialkylaminocrotonate (1)

Compound 1	Enamine	Reaction Conditions	Product, m.p., (% yield)
 1a	 4 a: n=1 b: n=2 c: n=3 d: n=4	TFA (2 mmol) /ClCH$_2$CH$_2$Cl (25 ml) /reflux/24 hrs.	 5 a: n=1,166-168° (64) b: n=2,158-159° (63) c: n=3,149-150° (59) d: n=4,157-159° (67)
 1a	 2 a: R=CH_3 b: R=C_2H_5 c: R,R=$(CH_2)_9$ d: R,R=$(CH_2)_{12}$	TFA (2 mmol) /100°/48 hrs	 3 a: R=CH_3,163-164°(41) b: R=C_2H_5,185-187°(37) c: R,R=$(CH_2)_9$,174-7° d: R,R=$(CH_2)_{12}$,201-4°
	 11 a: R=CH_3 b: R=C_2H_5		 12 a: R=CH_3, liq, (42) b: R=C_2H_5, liq, (36)
 1a	 9	TiCl$_4$ (1 mmol) /CH$_2$Cl$_2$ (5 ml) /-78° → rt/12 hrs	 10 77-78° (78)
 1b	 13		 14 108-109° (71)
	 15		 16 84-85° (-)

(Received in USA 5 April 1983)