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STUDIES ON as-TRIAZINE DERIVATIVES XIV[1]

SYNTHESIS AND REVERSE ELECTRON-DEMAND DIELS-ALDER REACTION OF ETHYL 5,8-DICHLORO-1,2,4-BENZOTRIAZINE-3-CARBOXYLATE

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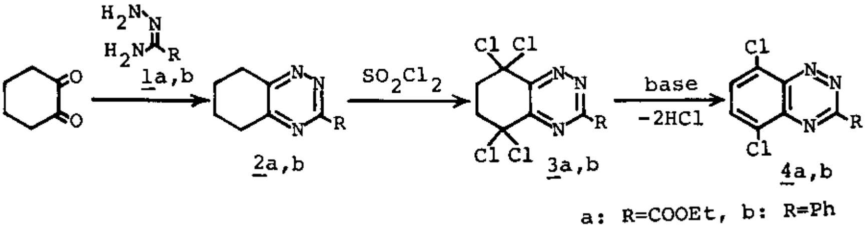
Abstract —— Ethyl 5,6,7,8-tetrahydro-1,2,4-benzotriazine-3-carboxylate was treated with sulfuryl chloride to give ethyl 5,5,8,8-tetrachloro-5,6,7,8-tetrahydro-1,2,4-benzotriazine-3-carboxylate. Following dehydrochlorination of the tetrachloro compound with triethylamine afforded ethyl 5,8-dichloro-1,2,4-benzotriazine-3-carboxylate. The dichloro-1,2,4-benzotriazine derivative was heated with norbornadiene in p-cymene to give ethyl 5,8-dichloroquinoline-2-carboxylate. Intramolecular Diels-Alder reaction of the dichloro-1,2,4-benzotriazine derivative was also investigated.

Recently, reverse electron-demand Diels-Alder reaction of monocyclic 1,2,4-triazine derivatives with electron-rich dienofiles has been developed as one of the most interesting parts of heteroaromatic chemistry.[2] The reaction is a facile route of access to some pyridine[3] and pyrimidine[4] derivatives, synthesis of which is not easily achieved by classical manners. In spite of the situation mentioned above, the Diels-Alder reaction of 1,2,4-benzotriazine derivatives has not reported prior to our present work. In this communication the authors describe a few examples of ring-transformation of 1,2,4-benzotriazines into quinolines by means of reverse electron-demand Diels-Alder reaction.

First of all, the synthesis of 5,8-dichloro-1,2,4-benzotriazine (**4a,b**) which was an major substrate in this investigation was accomplished as described below. When cyclohexane-1,2-dione was allowed to react with ethoxycarbonylformamidrazone

(**1a**) under conventional conditions,[5] 5,6,7,8-tetrahydro-1,2,4-benzotriazine-3-carboxylate (**2a**), bp_4 200°C(bath temp.), was obtained in 47 % yield. On treatment with excess sulfuryl chloride at room temperature, **2a** was readily chlorinated to give ethyl 5,5,8,8-tetrachloro-5,6,7,8-tetrahydro-1,2,4-benzotriazine-3-carboxylate (**3a**), mp 98-100°C, in almost quantitative yield. According to the similar manner, 5,5,8,8-tetrachloro-5,6,7,8-tetrahydro-3-phenyl-1,2,4-benzotriazine (**3b**), mp 146-148°C, was easily obtained starting from the condensation of cyclohexane-1,2-dione with benzamidrazone (**1b**). However, the chlorination of the corresponding 3-methylthio- and 3-methylsulfonyl derivatives (**2**; R=SMe and SO_2Me) gave resinous substances instead of desired tetrachlorides.



Scheme 1

In connection with the chlorination of **2a,b**, it was confirmed that 5,6-dialkyl-1,2,4-triazines were extremely reactive toward side-chain chlorination under these conditions. For example, when 5,6-dimethyl-3-phenyl-1,2,4-triazine was treated with chlorine in acetic acid, 6-dichloromethyl-5-trichloromethyl-3-phenyl-1,2,4-triazine was obtained as a sole product, and it is difficult to control this exhaustive side-chain chlorination.[6]

The tetrachlorides (**3a,b**) were dehydrochlorinated rapidly with an appropriate base, and 3-substituted 5,8-dichloro-1,2,4-benzotriazines (**4a,b**) were obtained as shown below.

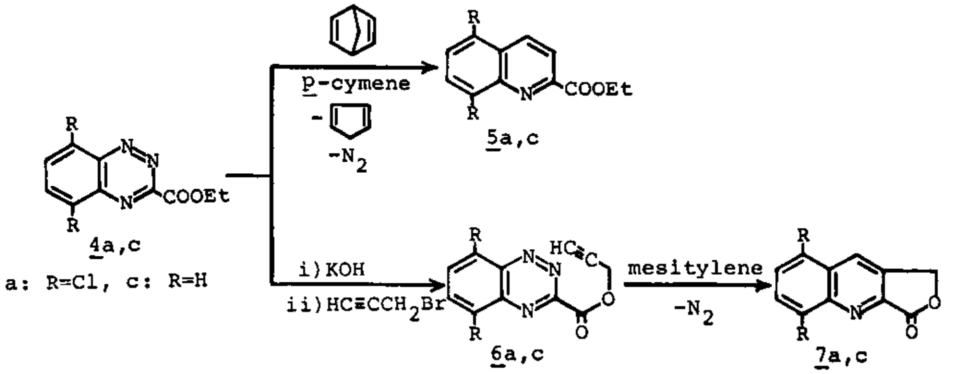
Conversion of 5,5,8,8-Tetrachloro-5,6,7,8-tetrahydro-1,2,4-benzotriazines (3a,b) to 5,8-Dichloro-1,2,4-benzotriazines(4a,b) with Base.

Compd No.	Base	Solvent	Reaction time (h)	Temperature	mp(°C)	Yield (%)
4a	Et_3N	EtOH-ether	0.5	room temp.	146-148	74
4b	NaOMe	MeOH-benzene	0.5	room temp.	208-210	86

There is no paper dealing with the aromatization of **2a,b** type compounds by means of conventional methods, so the transformation of **2a,b** to **4a,b** via **3a,b** may suggest a new method for the synthesis of 1,2,4-benzotriazine derivatives.[7]

Then, the reaction of 1,2,4-benzotriazine derivatives with dienofiles was investigated. When **4a** was heated with norbornadiene[8] in p-cymene under reflux (21 h), ethyl 5,8-dichloroquinoline-2-carboxylate (**5a**), mp 104-106°C, was obtained in 55 % yield. On the other hand, the reaction of ethyl 1,2,4-benzotriazine-3-carboxylate (**4c**)[9] with norbornadiene in boiling p-cymene gave ethyl quinoline-2-carboxylate in only 7 % yield in spite of prolonged reaction time (60 h). The advantage of dichloro substituents at 5- and 8-positions for the Diels-Alder reaction is also observed on intramolecular ring-transformation.

Namely, on heating in mesitylene for 13 h, propargyl 5,8-dichloro-1,2,4-benzotriazine-3-carboxylate (**6a**) derived from **4a** turned into dichloroquinoline lactone (**7a**) in 37 % yield, whereas the unsubstituted propargyl ester (**6c**) was resistant to the transformation, and the corresponding lactone was obtained by long time heating (33 h) in 18 % yield.



Scheme 2

The proposed structures of the final products (**7a,c**) are supported by the following spectral data.

7a: mp 233-235 °C, ir (KBr) cm^{-1}; 1770, ^{1}H-nmr (DMSO-d_6) δ ; 5.73 (2H, s), 7.93 (1H, d, J=8Hz), 8.13 (1H, d, J=8Hz), 9.03 (1H, s).

7c: mp 222-224 °C, ir (KBr) cm^{-1}; 1770, ^{1}H-nmr (DMSO-d_6) δ ; 5.66 (2H, s), 7.70-8.50 (4H, m), 8.75 (1H,s).

Although the reaction of **4b** with norbornadiene under similar conditions results in the formation of resinous substance, the presence of dichloro substituents at 5- and 8-positions in **4a** facilitates the Diels-Alder reaction. In order to clarify the role of the substituents, the Diels-Alder reaction of other 1,2,4-benzotriazines is under investigation.

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