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SYNTHESIS OF TRISUBSTITUTED 4H-1,2,4-OXADIAZINES[1),3)]

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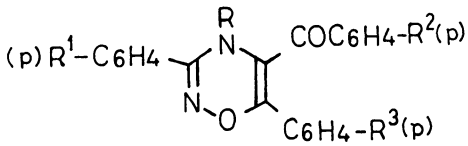
The derivatives of 4H-1,2,4-oxadiazine, a new class of six-membered heterocycles, were synthesized through the reactions of ß-diketones with aliphatic nitro compounds and acetyl chloride, and also of azirines with nitrile oxides. A reaction mechanism is proposed.

In this communication we wish to describe an one-step synthesis of a new heterocyclic compound, 4H-1,2,4-oxadiazine.[2)] When aliphatic nitro compounds(1) and acetyl chloride were allowed to react[4)] with ß-diketones(3), e.g. dibenzoylmethane, 5-benzoyl-3,6-disubstituted-4H-1,2,4-oxadiazine(6) was synthesized as follows: In a typical experiment, di-p-toluoylmethane[5)](3b) 516 mg(2.0 mmol) was added to a solution of p-tolylnitromethane[6)](1b) 602 mg(4.0 mmol) and acetyl chloride 0.29 ml(4.1 mmol) in N,N-dimethylacetamide(DMA) with three molar amount of sodium methoxide. The mixture was stirred at 80-85°C overnight. After neutralization with 1N hydrochloric acid and benzene extraction, further purification by chromatography of silica gel(benzene-ethyl acetate 20:1) were carried out. 5-p-Toluoyl-3,6-di-p-tolyl-4H-1,2,4-oxadiazine(6c) was obtained as colorless needles in a yield of 41%, which gave a singl spot on TLC; 6c: mp 238-241°C(from hexane-ethyl acetate), IR(KBr)ν_{max} cm^{-1}: 3260(NH), 1650(C=O); ^{1}H-NMR($CDCl_3$)δ: 7.42(NH); and the N-CH_3 derivative(7c) of 6c: mp 213-214°C, IR(KBr)ν_{max} cm^{-1}: νNH(disappeared), 1660(C=O); ^{1}H-NMR($CDCl_3$)δ: 3.45(3H, N-CH_3). This procedure was applied to the following aliphatic nitro analogs(1) and ß-diketones(3), i.e. 1: phenylnitromethane[7)](1a) and p-chlorophenylnitromethane[7)](1e); 3: dibenzoylmethane(3a). The oxadiazines(6a-6e) in question and their N-methyl derivatives[8)](7a-7d) were subsequently synthesized respectively. The results of extensive experiments are summarized in Table 1.

In order to confirm the reaction pathway, directly, a reaction of nitrile oxide with azirine was examined; both nitrile oxide and azirine were considered as the reaction-intermediates for further reactions. An equimolar reaction of 2-benzoyl-3-phenyl-2H-azirine(5a,[9)] R^2=R^3=H) with p-tolunitrile oxide(2b,[10)] R^1=CH_3) in DMA in the presence of 1N sodium methoxide proceeded easily to give the corresponding 5-benzoyl-6-phenyl-3-p-tolyl-4H-1,2,4-oxadiazine(6d), mp 188-190°C. This procedure was extensively applicable to the reaction of other 2 with 5. The results were also shown in Table 1.

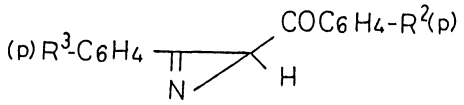
These results support the mechanism shown in Chart 1. As reported in our previous papers,[4)] the nitrile oxide(2) are generated by the O-acylation of nitro compounds(1) with acetyl chloride in DMA. Initially 2 (in situ) reacts with 3 to form an adduct 4

Table I. Yields, Melting Points, IR and ^{1}H-NMR Data of 4H-1,2,4-Oxadiazine Derivatives (6: R= H; 7: R= CH_3)



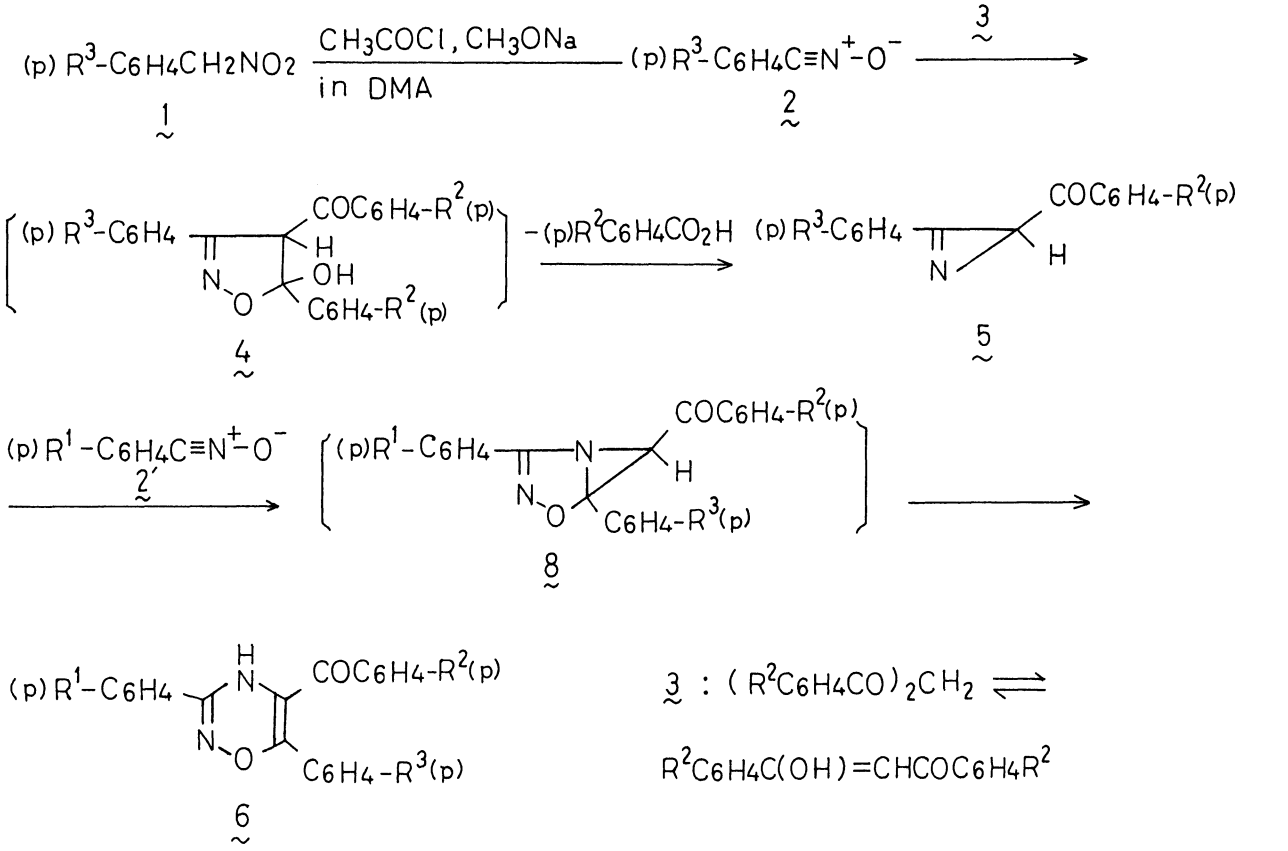
Compd.	R^1	R^2	R^3	Yield(%)			mp(°C)	IR(cm^{-1}) νNH	IR(cm^{-1}) νC=O	^{1}H-NMR NH	^{1}H-NMR N-CH_3
6a	H	H	H	16	—	(20)[b]	182-183	3210	1650	7.60	—
6b	CH_3	H	CH_3	28	(18)[a]	—	229-230.5	3240	1650	7.53	—
6c	CH_3	CH_3	CH_3	41	—	—	238-241	3260	1650	7.42	—
6d	CH_3	H	H	—	(13)[a]	(23)[b]	188-190	3240	1640	7.55	—
6e	Cl	H	H	—	—	(5)[b]	176-178	3260	1660	7.50	—
7a	H	H	H	92[c]	—	—	153-155	—	1660	—	3.47
7b	CH_3	H	CH_3	83[c]	—	—	176-178	—	1660	—	3.45
7c	CH_3	CH_3	CH_3	58[c]	—	—	213-214	—	1660	—	3.45
7d	CH_3	H	H	76[c]	—	—	155-157	—	1660	—	3.47

a) also prepared directly from isolated nitrile oxide(2b) and azirines(5a or 5b).
b) also prepared from azirine(5a) with the reaction mixture of 1 and acetyl chloride.
c) yield of 7 from 6 through N-methylation.



5a, R^2=R^3= H; 5b, R^2= H, R^3= CH_3

Chart 1

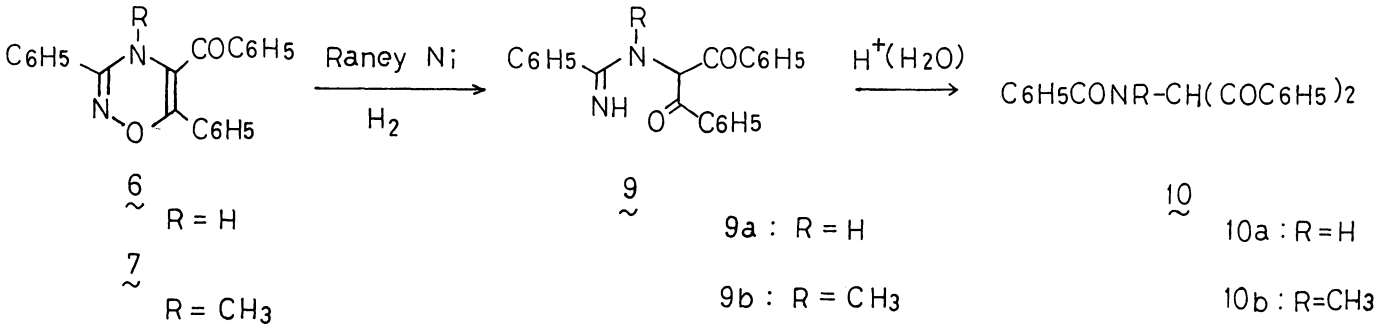


by 1,3-cycloaddition reaction which gives azirine(5) by elimination of benzoic acid. Furthermore, 5 reacts with an other 2 to furnish the expected cycloadduct 8.[11] This fused aziridine adduct 8 undergoes ring expansion through participation of the carbon-nitrogen bond of aziridine ring, of which cleavage induces a rearrangement of methine proton at C-5 to the N-4 position by nucleophilic methoxide ion. Finally, the 4H-oxadiazine(6) is given.[12]

Chemical evidence in support of structure 6 includes the following reactions: Ring opening of 6a occurred by Raney Ni(T-1) under hydrogen at atomospheric pressure in MeOH to lead an iminomethyl derivative(9) of α-aminodibenzoylmethane as the main product, and after acid-hydrolysis by 1N hydrochloric acid, the resulted product of 9 proved identical with an authentic sample of N-benzoyl-dibenzoylmethane[13](10a) which was synthesized independently. In the same manner, hydrogenation and further hydrolysis of N-methyl derivative(7) also gave the corresponding reaction products, 9b, mp 211-213°C(methanol-hexane), and 10b, mp 130-132°C(methanol), respectively. These products were identified as expected products by elemental analysis, as well as ir, nmr, and MS analyses (Chart 2).

A further detailed study on the synthesis of new member of above-heterocycles is now in progress.

Chart 2



6 R = H

7 R = CH3

9 9a : R = H

9b : R = CH3

10 10a : R = H

10b : R = CH3

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3) Melting points are uncorrected; ^{1}H-NMR spectra were measured using TMS as an internal standard.

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8) Methylation of 6c by methyl iodide gave the corresponding N-methyl derivative(7c). Similarly 7d (Table 1) from 6d.

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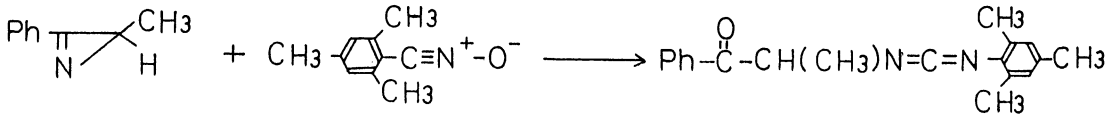
12) In a similar study, Nair(Tetrahedron Lett., 1971, 4831) reported that azirine(i) reacts with 2,4,6-trimethylbenzonitrile oxide(ii) in ether at 0°C to furnish carbodiimide(iii) exclusively.



(i) (ii) (iii)

This reaction is closely related to the method reported in this communication. Whereby, however, 4H-oxadiazine derivatives are obtained instead.

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