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SYNTHESIS OF 3,5,6-TRISUBSTITUTED 1,2,4-TRIAZINES FROM 3,6-DISUBSTITUTED 1,2,4,5-TETRAZINES AND N-(TRIMETHYLSILYL)BENZALDIMINES

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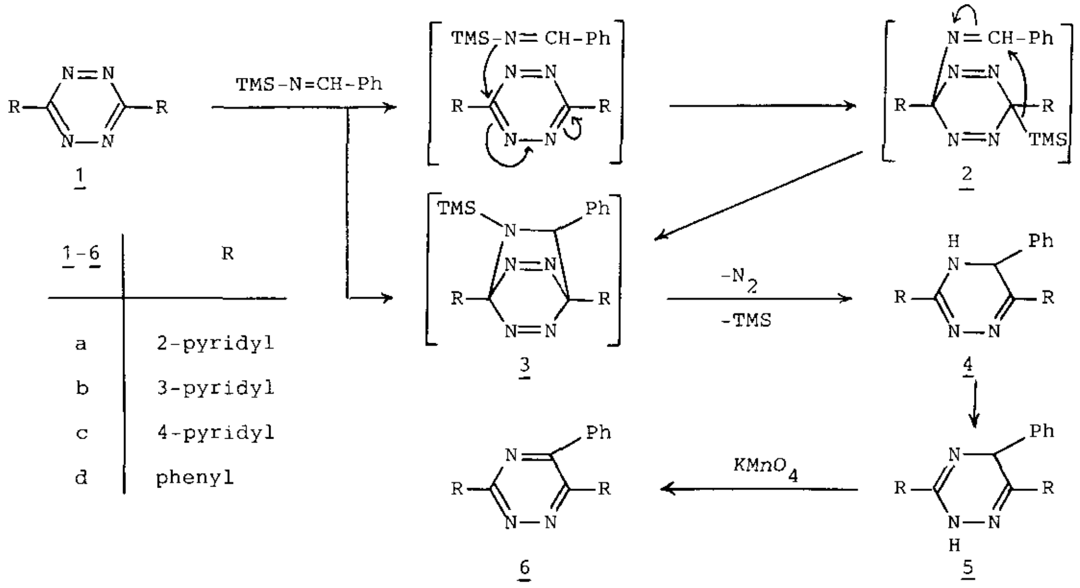
Abstract ——Reaction of 3,6-disubstituted 1,2,4,5-tetrazines (1) with N-(trimethylsilyl)benzaldimine gave 3,5,6-trisubstituted 2,5-dihydro-1,2,4-triazines (5), which were oxidized with potassium permanganate to afford 3,5,6-trisubstituted 1,2,4-triazines (6).

We have recently reported two ring transformation reactions of 1,2,4,5-tetrazines (1) by the use of organosilicon reagents: 1 reacted with cyanotrimethylsilane in toluene or xylene under reflux to give 4-amino-1-arylmethylpyrazoles incorporating the solvents,[1] while the reaction of 1 with isocyanato- or isothiocyanatotrimethylsilane afforded 1,2,4-triazin-5-ols or -5-thiols, respectively.[2] The formation of these products could be explained in terms of initial nucleophilic attack by the cyano, isocyanato, or isothiocyanato anions on the C-2 atom of the tetrazine ring followed by cyclization and subsequent loss of nitrogen. As an extension of this work we have chosen this time N-(trimethylsily)imines as the organosilicon reagents since it is known that they behave as nucleophiles towards heterocumulenes ,[3] imidoyl chlorides,[4] aldehydes,[5] nitrones,[6] acyl chlorides,[7] and activated acetylenes.[8]

A mixture of 3,6-diaryl-1,2,4,5-tetrazines (1a-d) and N-(trimethylsilyl)benzaldimines[9] in toluene was refluxed for 12-50 h under nitrogen atmosphere to give 3,6-diaryl-5-phenyl-2,5-dihydro-1,2,4-triazines (5a-d) in 29-61% yields.

A possible mechanism giving rise to the products is envisaged as follows: a nucleophilic attack of the imino nitrogen of the reagent on the ring carbon of 1 affords 2, which undergo cyclization to yield the bicyclic intermediates 3.



1-6	R
a	2-pyridyl
b	3-pyridyl
c	4-pyridyl
d	phenyl

Extrusion of nitrogen from 3 results in the formation of 4,5-dihydro-1,2,4-triazines 4, which would isomerize by 1,3-hydrogen shift to 2,5-dihydro-1,2,4-triazines 5 (a proof of the structure 5 is given below). However, an alternative pathway from 1 to 3 must be considered since 1,2,4,5-tetrazines[10] are well known azadienes with inverse electron demand in Diels-Alder reaction.[11] Activated carbon-nitrogen double bonds such as imidates, amidines, thioimidates, hydrazones, or azirines can participate in [4+2]cycloaddition reactions.[11] Accordingly, a possibility of cycloaddition of 1 to N-(trimethylsilyl)imine to form 3 directly remains at the present stage.

Alkyl and aryl substituted 1,2,4-triazines are conveniently prepared by condensation of 1,2-dicarbonyl compounds with amidrazones $R\text{-}C(NH_2)\text{=}NNH_2$.[12] However, synthesis of 1,2,4-triazines having different substituents at the 5 and 6 positions is difficult since unsymmetrical 1,2-dicarbonyl compounds often lead to a mixture of two positional isomers. Recently Konno et al.[13] have solved this problem by addition of Grignard reagents to the 5-position of 3,6-disubstituted 1,2,4-triazines followed by oxidation of the resulting 3,5,6-trisubstituted 2,5-dihydro-1,2,4-triazines. Oxidation of 5 would provide a new route to this class of compounds. In fact, treatment of 5a-d with potassium permanganate in acetone at room temperature gave 6a-d in 54-91% yields.

Reduction of 1,2,4-triazines with sodium borohydride is reported to yield 2,5-dihydro-1,2,4-triazines selectively.[14] Treatment of 6a in the same manner with

Table. Physical and Spectral Properties of Compounds 5 and 6

Compound	Yield %	Mp (°C) Solvent	Molecular Formula	Found (Calcd) C%	H%	Ms m/z, M$^+$	Ir KBr, cm^{-1}		
5a	52	215-217	$C_{19}H_{15}N_5$	73.17	4.89	313	3310	3050	1630
		C_6H_6	(313.35)	(72.82	4.83)		1580	1560	1455
5b	61	207-209	$C_{19}H_{15}N_5$	72.77	4.97	313	3300	3050	1610
		EtOH	(313.35)	(72.82	4.83)		1580	1560	1490
5c[15]	40	171-173	$C_{19}H_{15}N_5$	73.14	5.03	313	3350	3040	1620
		C_6H_6	(313.35)	(72.82	4.83)		1590	1550	1510
5d	29	245-247	$C_{21}H_{17}N_3$	81.18	5.49	311	3280	3040	1605
		toluene	(311.29)	(81.00	5.50)		1565	1490	1450
6a	83	161-163	$C_{19}H_{13}N_5$	73.14	4.20	311	3060	1580	1570
		$CHCl_3$-hexane	(311.33)	(73.29	4.21)		1500	1490	1460
6b	91	181-183	$C_{19}H_{13}N_5$	72.99	4.25	311	3070	1580	1570
		$CHCl_3$-hexane	(311.33)	(73.29	4.21)		1500	1490	1430
6c	55	202-204	$C_{19}H_{13}N_5$	73.42	4.34	311	3040	1590	1550
		$CHCl_3$-hexane	(311.33)	(73.29	4.21)		1480	1390	1360
6d	54	147-148 (lit.[16] mp 142-144°C)				309	3050	1485	1440
		C_6H_6-hexane					1430	1380	1360

sodium borohydride gave 5a in 82% yield, indicating the structure of dihydro-1,2,4-triazines in the present study to be 2,5-dihydro-1,2,4-triazines (5).

EXPERIMENTAL

3,5,6-Trisubstituted 2,5-dihydro-1,2,4-triazines (5a-d)

A general procedure. A mixture of 1 (2.0 mmol) and N-(trimethylsilyl)benzaldimine[9] (5.0 mmol) in toluene (15 ml) was refluxed under nitrogen atmosphere for 12-50 h. The reaction was completed by adding an additional amount of the imine and prolonged heating if necessary by following the reaction on tlc. After evaporation of the solvent the residue was washed with MeOH or EtOAc and recrystallized to give 5.

3,5,6-Trisubstituted 1,2,4-triazines (6a-d)

A general procedure. To a stirred mixture of finely ground $KMnO_4$ (2.0 mmol) in acetone (30 ml), 5 (1.0 mmol) was added and the mixture was further stirred at room temperature for 6-12 h. The reaction was completed by adding an additional amount of $KMnO_4$ and prolonged stirring if necessary by following the reaction on tlc. After quenching with MeOH the solvent was removed and the residue was extracted with hot $CHCl_3$. The extract was washed with water, dried over Na_2SO_4, and evaporated to give a residue, which was recrystallized to afford yellow product 6. In the case of 6c and d the residue was chromatographed on silica gel with an eluent of $CHCl_3$ using a short column.

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