Cycloaddition Reactions of Cyclic Ketene-*N,S*-Acetals with 1,2,4,5-Tetrazines

Antonius T. M. Marcelis and Henk C. van der Plas*

Department of Organic Chemistry, Agricultural University, De Dreijen 5,
6703 BC Wageningen, The Netherlands

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Reaction of 3,6-diphenyl-, 3,6-bis(2-pyridyl)- and the unsubstituted 1,2,4,5-tetrazine with 4,5-dihydro-1-methyl-2-(methylthio)pyrrole (**2**) and 1-methyl-2-(methylthio)-4,5,6,7-tetrahydroazepine (**3**) gives 4,7-di-*R*-2,3-dihydro-1-methylpyrrolo[2,3-*d*]pyridazine (**4**, R = phenyl, 2-pyridyl, hydrogen) and 6,9-di-*R*-1-methyl-2,3,4,5-tetrahydropyridazino[4,5-*b*]azepine (**5**), R = phenyl, 2-pyridyl, hydrogen), respectively, in reasonable to good yields. The compounds **4** (R = phenyl, hydrogen) are converted into their corresponding 1-methylpyrrolo-[2,3-*d*]pyridazines **6** by reaction with potassium permanganate in butanone. Reaction of 3-phenyl-1,2,4,5-tetrazine with **2** and **3** leads to the exclusive formation of the 7-phenyl isomer **4d** and 9-phenyl isomer **5d**, respectively, indicating that the cycloaddition is regiospecific. The mechanism is discussed.

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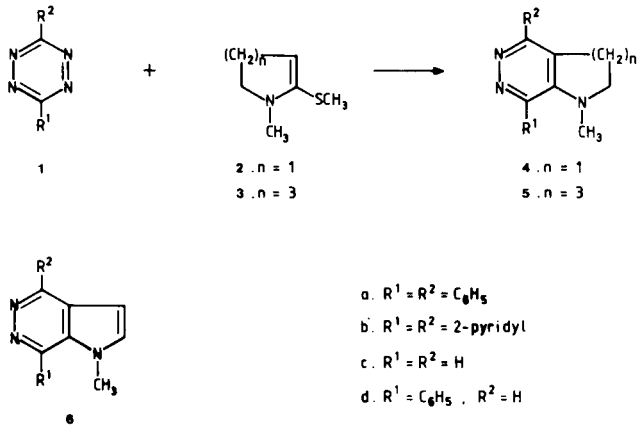
In recent years there has been an increased interest in inverse electron-demand Diels-Alder reactions with heterocycles. Mainly, the reactions of tetrazines and triazines with a vast number of alkenes and alkynes have been investigated [1,2]. More recently, some pyrimidines containing electron-withdrawing groups have also been found to react with electron-rich alkenes and alkynes like enamines and ynamines [3,4,5]. Only a few studies have been directed towards the regioselectivity of the cycloaddition with 1,2,4,5-tetrazines and triazines [6,7]. Since we were interested in the preparation of bicyclic systems, containing a pyridazine ring, we investigated the reaction of tetrazines with cyclic *N,S*-acetals **2**, **3** and studied the regioselectivity of the addition reaction.

Reaction of diphenyltetrazine (**1a**) with 4,5-dihydro-1-methyl-2-(methylthio)pyrrole (**2**) at room temperature gave 2,3-dihydro-4,7-diphenyl-1-methylpyrrolo[2,3-*d*]pyridazine (**4a**) in good yield (see Table 1). A similar reaction, although more slowly, took place with 1-methyl-2-(methylthio)-4,5,6,7-tetrahydroazepine (**3**), yielding 6,9-diphenyl-1-methyl-2,3,4,5-tetrahydropyridazino[4,5-*b*]azepine (**5a**). During both reactions nitrogen and methylmercaptan were evolved. No indications for the formation of a pyridazine derivative were obtained containing a (methylamino)-alkylene side-chain. This result shows that the breakage of the C-S bond is preferred to C-N bond breakage; this was also observed in the reactions of 1,2,4-triazines and tetrazines with acyclic ketene-*N,S*-acetals [6,7].



Bis(2-pyridyl)-1,2,4,5-tetrazine (**1b**) also reacts easily with the ketene acetals **2** and **3**, yielding the corresponding **4b** and **5b**, respectively.

We also included in our study the reaction of the parent 1,2,4,5-tetrazine (**1c**) with **2** and **3**. Although the parent system **1c** has been known for a long time, to our knowledge, no inverse electron-demand Diels-Alder reactions with this compound have been reported. Reaction of **1c** with **2** and **3** gave the compounds **4c** and **5c** in reasonable-to-good yield (Table 1).

The dihydro compounds **4a** and **4c** could be aromatized by reaction with potassium permanganate in butanone, the 1-methylpyrrolo[2,3-*d*]pyridazines **6a** and **6c** being obtained. Compound **6c** is a known compound and the physical data are in agreement with those reported in the literature [8,9].

Comparison of the ^{1}H-nmr spectra of **4a-c** and **5a-c** shows that the *N*-methyl protons in **4a,b** and **5a,b** are shielded compared to the *N*-methyl protons in **4c** and **5c** by the sterically nearby aromatic substituent on the pyridazine ring. This shielding effect is stronger in the compounds **5a,b** than a **4a,b**. Furthermore, a small coupling of about 1 Hz is observed between H4 and the CH_2-protons at C3 in **4c**. The ^{13}C-nmr chemical shift value of C4 in **4a-c** is higher than that of C7. The presence of an aromatic ring at C4 or C7 leads to a downfield shift of about 6-12 ppm, compared to the chemical shift values of C4 and C7 in **4c**. The same observations were found for the ^{13}C-chemical shift data of C6 and C9 in the compounds **5a-c** (Table 2).

Table 1

Analytical and Physical Data of the Compounds **4**, **5** and **6**

Compounds	R^1	R^1	Yield (%)	Mp (°C)	Molecular Formula	% C (Calcd.)	% H (Calcd.)	MS (M^+)
4a	Ph	Ph	93	146-147	$C_{19}H_{17}N_3$	79.67 (79.41)	5.73 (5.96)	287
4b	2-Py	2-Py	40	136-138	$C_{17}H_{15}N_5$	70.13 (70.57)	5.06 (5.23)	289
4c [a]	H	H	70	52-53	$C_{17}H_{19}N_3O_{1/2}$	58.08 (58.31)	6.90 (6.99)	135
4d	Ph	H	81	91-92	$C_{13}H_{13}N_3$	73.97 (73.90)	6.08 (6.20)	211
5a	Ph	Ph	70	138-139	$C_{21}H_{21}N_3$	79.69 (79.97)	6.42 (6.71)	315
5b	2-Py	2-Py	85	148-149	$C_{19}H_{19}N_5$	71.66 (71.90)	5.73 (6.03)	317
5c [b]	H	H	64	160-161	$C_{15}H_{16}N_6O_7$	46.02 (45.92)	3.92 (4.11)	163
5d	Ph	H	56	133-134	$C_{15}H_{16}N_3$	75.59 (75.28)	6.83 (7.16)	239
6a	Ph	Ph	36	241-242	$C_{19}H_{15}N_3$	79.82 (79.97)	5.28 (5.30)	285
6c [c]	H	H	35	111-112	$C_7H_7N_3$			

[a] Crystals of this compound were isolated as the hemihydrate; ms: m/e 135.0792; Calcd. 135.0796. [b] This compound was obtained as an oil; the mp and analyses are given of the picrate ($C_9H_{13}N_3 \cdot C_6H_3N_3O_7$); ms: m/e 163.1101; Calcd. 163.1109. [c] Lit [13] mp 111°.

Table 2

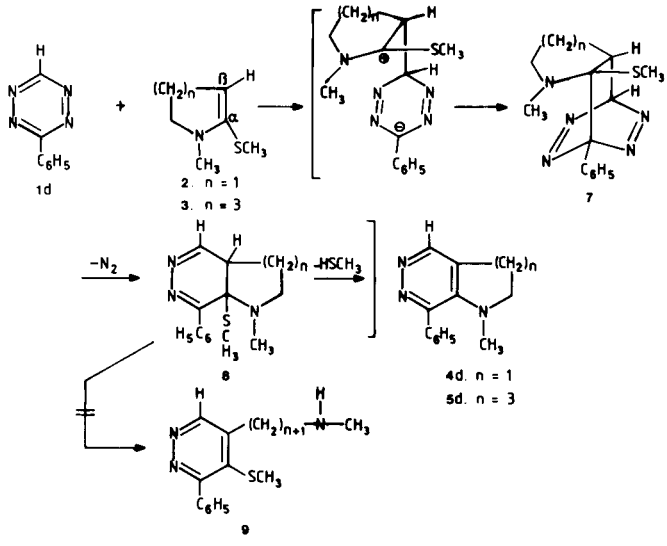
Spectroscopic Data of Compounds **4** and **5**

Compound	^{1}H-NMR			^{13}C-NMR (J)				
	N-CH_3	H_4	H_7	N-CH_3	C_4	C_7	C_{3a}	C_{7a}
4a	2.50	—	—	37.9	154.1	144.7	126.1	149.9
4b	2.67	—	—	37.9	151.7	143.1	129.2	150.6
4c	2.83	8.50	8.37	32.8	145.4 (177)	132.8 (181)	126.9	150.3
4d	2.42	8.57	—	37.0	145.1 (177)	145.6	125.1	148.9
	N-CH_3	H_6	H_9	N-CH_3	C_6	C_9	C_{5a}	C_{9a}
5a	2.37	—	—	41.6	160.4	154.4	130.6	147.7
5b	2.34	—	—	41.9	158.7	153.2	131.8	148.2
5c	3.02	8.47	8.60	40.4	151.1 (176)	140.0 (179)	126.0	148.4
5d	2.38	8.61	—	41.2	151.3 (178)	155.4	131.0	147.8

In the reaction of the asymmetrically substituted 3-phenyltetrazine **1d** with **2** and **3** respectively, the formation of only one product is observed; it indicates that in these reactions the cycloaddition is regiospecific. Comparison of the nmr data of the compound obtained from the reaction of **1d** with **2**, with those of the compounds **4a-c** led us to assign the position of the phenyl group at C-7, *i.e.* isomer **4d**. A distinct shielding is observed for the *N*-methyl protons of **4d**, indicating that this group is in the vicinity of the phenyl group. The observed coupling of about 1 Hz for the aromatic proton of **4d** and the downfield shift of C7 and not of C4 in the ^{13}C-nmr spectra confirm structure **4d**. Based on similar considerations the product obtained in the reaction of **1d** with **3** was assigned structure **5d**.

We explain the regioselectivity of the addition by assuming that the reaction is sterically controlled. Because C6 of **1d** is unsubstituted, attack by the electron-rich ß-carbon atom of the ketene-*N,S*-acetals preferentially occurs at the least sterically hindered site of the tetrazine, *i.e.* C6. In the bipolar transition state a fast bond formation between C3 of the tetrazine and the α-carbon atom of the ketene acetal takes place. This leads to the tricyclic intermediate **7**, from which by extrusion of nitrogen the bicyclic compound **8** is obtained. Aromatization of the dihydro compound by loss of methylmercaptan then leads to the bicyclic compounds **4d** or **5d**. This probably occurs according to an E_1 mechanism, since *trans*-elimination of methylmercaptan is unlikely from compound **8**. Aromatization of **8** through ring opening of the saturated five- or seven-membered ring

leading to **9** is not observed; the weaker C-S bond is more easily broken (see Scheme).



Scheme

2,3-Dihydro compounds of type **4** and **5** are rarely described in the literature [10,11] and their chemistry has not been much investigated, in contrast to the fully aromatic pyrrolo[2,3-*d*]pyridazines, which show potential antineoplastic activity [12]. The reactions described in this paper offer a good route to various substituted compounds of type **4** and **5**.

EXPERIMENTAL

Melting points are uncorrected. The ^{1}H-nmr spectra (deuteriochloroform) were recorded with a Varian EM-390 90-MHz spectrometer using tetramethylsilane as an internal reference. ^{13}C-nmr spectra were recorded with a Bruker CXP-300 spectrometer. Mass spectra were obtained with a JEOL JMS-D-100 spectrometer. Analytical data of the compounds **4**, **5** and **6** are summarized in Tables 1 and 2. The starting materials diphenyltetrazine (**1a**) [13], bis(2-pyridyl)tetrazine (**1b**) [14], phenyltetrazine (**1c**) [15], 4,5-dihydro-1-methyl-2-(methylthio)pyrrole (**2**) [16] and 1-methyl-2-(methylthio)-4,5,6,7-tetrahydroazepine (**3**) [16] are prepared according to procedures described in the literature. 1,2,4,5-Tetrazine was prepared by a modification of the procedure described by Lang *et al.* [15] for the synthesis of monosubstituted tetrazines.

Synthesis of 1,2,4,5-tetrazine (**1c**).

To 31.2 g (0.3 mole) of formamidine acetate, cooled in ice, are slowly added 40 ml (0.8 mole) of hydrazine hydrate. The resulting mixture is stirred for 1 hour at room temperature. After addition of 20 ml of water and stirring at 0° for 1 hour, the precipitate is filtered under nitrogen and sucked as dry as possible. The precipitate is dissolved in 100 ml of acetic acid and 10 g of sodium nitrite is added in small portions at about 5°. After stirring for 1 hour, 150 ml of water are added and the mixture is extracted four times with 150 ml of dichloromethane. The combined dichloromethane layers are washed with sodium hydrogen carbonate solutions until neutral, dried on magnesium sulfate and concentrated to about 10 ml. Column chromatography on silica gel with dichloromethane and concentration of the red band gives 4.2 g 1,2,4,5-tetrazine (**1c**), yield 34%.

General Procedure for the Synthesis of the 2,3-Dihydro-1-methylpyrrolo-[2,3-*d*]pyridazines **4**.

To a stirred solution of 1 mmole of the appropriate 1,2,4,5-tetrazine in 10 ml of dichloromethane a solution of 1.5 mmoles of 4,5-dihydro-1-methyl-2-(methylthio)pyrrole (**2**) in 5 ml of dichloromethane is added dropwise. The red colour of the tetrazine disappears within a few minutes. The reaction mixture is concentrated and the product is isolated by column chromatography on silica gel using ethyl acetate/methanol mixtures as eluent. The compounds are recrystallized from diisopropyl ether.

General Procedure for the Synthesis of the 1-Methyl-2,3,4,5-tetrahydropyridazino[4,5-*b*]azepines **5**.

A solution of 2 mmoles of 1-methyl-2-(methylthio)-4,5,6,7-tetrahydroazepine (**3**) in 5 ml of dichloromethane is added under nitrogen to a solution of 1 mmole of the appropriate 1,2,4,5-tetrazine in 10 ml of dichloromethane. The mixture is refluxed for 1 to 4 hours until the red colour of the tetrazine has disappeared. The reaction mixture is concentrated and the product is isolated by column chromatography on silica gel using ethyl acetate/methanol mixtures as eluent. The compounds are recrystallized from diisopropyl ether, except **5c**, which is obtained as an oil.

General Procedure for the Oxidation of the Compounds **4a**, **4c** into the 1-Methylpyrrolo[2,3-*d*]pyridazines **6a** and **6c**.

To a stirred solution of 1 mmole of the 2,3-dihydropyrrolo[2,3-*d*]pyridazine **4a,c** in 20 ml of butanone, 1 g of potassium permanganate is added. The stirred mixture is refluxed until the starting material has disappeared according to tlc. If necessary, extra portions of potassium permanganate are added. The solid material is filtered and washed with acetone. The filtrate is concentrated and the product is purified by column chromatography on silica gel using ethyl acetate/methanol 4:1 as eluent. The products are recrystallized from toluene/hexane.

Compound **6a**.

This compound had ^{1}H-nmr: 8.15-7.45 (10H, phenyl), 7.22 (1H, J = 3.2 Hz, H2), 6.87 (1H, H3), 3.48 (3H, N-CH$_3$); ^{13}C-nmr: 36.7 (N-CH$_3$).

Compound **6c**.

This compound had ^{1}H-nmr: 9.38 (1H, H4), 9.28 (1H, H7), 7.28 (1H, J = 3.0 Hz, H2), 6.62 (1H, H3), 3.92 (3H, N-CH$_3$).

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