SYNTHESES AND REACTIONS OF PYRIDAZINE DERIVATIVES XX[1]
STUDIES ON THE RADICAL METHYLATION OF THE 1,2-DIAZINE SYSTEM

Gottfried Heinisch* and Gerhard Lötsch
Institut für Pharmazeutische Chemie, Universität Wien
Währingerstraße 10, A-1090 Vienna, Austria

Abstract —— Protonated pyridazines (1,2,3) on reaction with methyl radical (generated by oxidative decarboxylation of acetic acid or by redox reaction of t-BuOOH/$FeSO_4 \cdot 7H_2O$) are shown mainly to be attacked at positions ß to the nitrogen atoms. However, formation of compounds 2,4,5,6,8,9 and 10 indicates lower degree of regioselectivity compared with homolytic benzylation or acylation of the 1,2-diazine system. Synthesis of ethyl 5-styryl-4-pyridazinecarboxylates(13,14)was achieved by homolytic methylation of ethyl 4-pyridazinecarboxylate(11) followed by condensation with aromatic carbaldehydes.

In spite of the fact that the "Minisci" reaction[2] has, due to its high selectivity and versatility, attracted much attention in heterocyclic chemistry during the last decade, there are, to our knowledge, only a few reports[3-13] dealing with this type of substitution reactions of the protonated 1,2-diazine system.

We describe herein investigations of reactions of protonated pyridazine (1), methylpyridazines 2 and 3 and ethyl 4-pyridazinecarboxylate(11) with methyl radical generated by Ag^+-catalyzed oxidative decarboxylation of acetic acid with peroxydisulphate[5] (method A) or by redox process of t-BuOOH/$FeSO_4 \cdot 7H_2O$[14] (method B), respectively.

As can be seen from results listed in Tables 1 and 2, reactions of 1,2 and 3 yield, in contrast to findings with photo-induced radical methylation of pyridazines,[6] mixtures, containing all of the theoretically possible C-methylated pyridazines.[15] Compounds 1-10, all known from literature,[6,16-21] could be separated by means of GLC. They were identified by their behaviour in gas-chromatographic analysis and their spectroscopic (ms, nmr) characteristics.

Table 1: Reaction of Pyridazine (1) with Methyl Radical

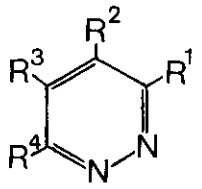
		% ratio of products (% yield[a]) method A[b]		method B[c]	
compd.	refs.	exp.1	exp.2[d]	exp.3[e]	exp.4[f]
1	16	1 /	- /	24 /	2 /
2	17	2 (2)	- (-)	7 (9)	2 (2)
3	18	17 (18)	- (-)	45 (60)	21 (21)
4	19	12 (12)	- (-)	6 (8)	12 (12)
5	20	7 (7)	- (-)	3 (4)	7 (7)
6	21	<1 (<1)	- (-)	<1 (<1)	<1 (<1)
7	19	29 (29)	2 (2)	12 (16)	32 (33)
8	6	25 (25)	50 (50)	2 (3)	20 (20)
9	21	3 (3)	- (-)	- (-)	2 (2)
10	21	2 (2)	48 (48)	- (-)	2 (2)

Table 2: Reactions of 3-Methylpyridazine (2) and 4-Methylpyridazine (3) with Methyl Radical (method A[b])

	% ratio of products (% yield[a])		% ratio of products (% yield[a])	
compound	obtained from 2:		obtained from 3:	
2	<1	/	-	(-)
3	-	(-)	2	/
4	8	(8)	4	(4)
5	5	(5)	2	(2)
6	<1	(<1)	-	(-)
7	-	(-)	27	(28)
8	55	(55)	52	(53)
9	6	(6)	2	(2)
10	26	(26)	10	(10)

a) yields based on converted base; b) Ag^{+}-catalyzed oxidative decarboxylation of acetic acid;[5] c) redox reaction of t-BuOOH/$FeSO_4 \cdot 7H_2O$;[14] d) methylation of the reaction mixture obtained from exp.1; e) t_{max}=15°C; f) t_{max}=25°C;

	R^1	R^2	R^3	R^4
1	H	H	H	H
2	CH_3	H	H	H
3	H	CH_3	H	H
4	CH_3	CH_3	H	H
5	CH_3	H	CH_3	H
6	CH_3	H	H	CH_3
7	H	CH_3	CH_3	H
8	CH_3	CH_3	CH_3	H
9	CH_3	CH_3	H	CH_3
10	CH_3	CH_3	CH_3	CH_3



	R^1	R^2	R^3	R^4
11	H	$COOC_2H_5$	H	H
12	H	$COOC_2H_5$	CH_3	H
13	H	$COOC_2H_5$	CH=CH-Ph	H
14	H	$COOC_2H_5$	CH=CH-(2,4-di-Cl)-Ph	H

In agreement with results obtained by Tsuchiya et al.[6] and other related reactions previously reported,[3-13,22] experiments (shown in Tables 1 and 2) again indicate, that, unlike other π-deficient heteroaromatics studied,[2] the 1,2-diazine system is attacked mainly by nucleophilic carbon radicals at positions 4 and 5, respectively and not at the positions of lowest electron densities, α to the nitrogen atoms. However, in contrast to homolytic benzylation[8] or acylation,[9,11,13] there is a marked lack of regioselectivity in homolytic methylation, as can be seen from formation of 2,4,5,6 and 9 in the reactions of 1,2 and 3. Furthermore in compounds 7 and 8, where positions 4 and 5 are occupied by substituents, positions 3+6 and 6 are attacked to a considerable degree. There is additional evidence for this fact, that repeated reaction of the mixture obtained from exp.1 (Table 1) almost exclusively leads to formation of 8 and 10 (Table 1, exp.2).

Whereas method A (base:persulphate ratio 1:3) leads to almost quantitative conversion of the heteroaromatics, homolytic methylation of 1, using method B (base:peroxide ratio 1:3, 15°C[14]), was found to result in only 76% conversion of 1 (Table 1, exp.3). However, reacting 1 at a maximum temperature of 25°C (exp.4) permits a 98% conversion. Evidently there is almost no difference in ratio of products thus obtained, compared with the results from exp.1. Thus the lower reaction temperature of method B seems to be more suitable for preparation of C-methylated pyridazines containing additional functional groups, e.g. alkyl 5-methyl-4-pyridazinecarboxylates, being of interest in syntheses of 4,5-annulated 1,2-diazines. This assumption is supported by the fact, that in the reaction of 11 (Table 3) the ester group was not affected, using method B.

Table 3: Reaction of Ethyl 4-pyridazinecarboxylate(11) with Methyl Radical (method B[a])

compound	% ratio of products exp.5[c]	exp.6[d]	(% yield[b]) exp.7[e]	molec. weight (from ms)
11	26 /	- /	7 /	
12	64 (86)	38 (38)	68 (73)	166
dimethylated compd.	4 (6)	15 (15)	7 (8)	180
dimethylated compd.	6 (8)	41 (41)	17 (18)	180
trimethylated compd.	- (-)	6 (6)	1 (1)	194

a)redox reaction of t-BuOOH/$FeSO_4 \cdot 7H_2O$,[14] b)yields based on converted base; *c)base:peroxide ratio 1:3; d)methylation of the reaction-mixture obtained from* exp.5, base:peroxide ratio 1:3; e)base:peroxide ratio 1:4;

As shown by GLC, ethyl 5-methyl-4-pyridazinecarboxylate(12) is formed in 64% yield, with a 74% conversion of 11. Raising conversion rate (by alteration of base:peroxide ratio or by repeated methylation of the reaction mixture obtained) is not accompanied by an increase of the yield of 12 due to increased formation of di- and trimethylated products (Table 3, exps.6,7).
Attempts to separate methylated ethyl 4-pyridazinecarboxylates in a preparative scale failed. The structure of 12, however, was confirmed on the basis of ms and nmr data and furthermore by conversion to well defined compounds 13 and 14.
Thus homolytic methylation of 11, followed by condensation with aromatic carbaldehydes, provides an efficient method for the preparation of hitherto unknown (E)-ethyl 5-styryl-4-pyridazinecarboxylates.

EXPERIMENTAL

Melting points (uncorrected) were determined with a Kofler apparatus. Ir spectra were recorded on a Jasco IRA-1 spectrometer (KBr disks; ν_{max} in cm^{-1}). ^{1}H-nmr spectra were recorded with a Varian EM 390 (90MHz), with $CDCl_3$ as solvent; chemical shifts (J in Hz) are reported in ppm downfield from internal TMS. Mass spectra were obtained on a Finnigan 4500 or Varian MAT CH-7. Microanalyses were performed by the "Institut für Physikalische Chemie" (University of Vienna, Dr. Zak). GLC analyses were carried out with a Varian VAE 3700 (N_2, 30ml/min; FID); 1.5m x 6.35mm glass columns, packed with 3% amine 220 on Chromosorb W or 3% OV 17 on Chromosorb WAW, respectively, were used.

Reaction of Pyridazine (1), 3-Methylpyridazine (2) and 4-Methylpyridazine (3) with Methyl Radical (method A)

To a stirred solution of 1 (0.8g, 0.01mol), acetic acid (3.0g, 0.05mol), $AgNO_3$ (0.51g, 0.003mol) in 10% aq. H_2SO_4 (10ml) at 90°C a solution of $(NH_4)_2S_2O_8$ (6.85g, 0.03mol) in 15ml H_2O was added dropwise over a period of 10 min. Heating was continued for another 60 min. The solution was cooled to 0°C, basified with conc. NH_4OH and extracted with CH_2Cl_2. After removal of solvent in vacuo the residue was analyzed by GLC (amine 220).

The reactions of 2 and 3 as well as repeated methylation of products obtained from exp.1 (cf. Table 1) were carried out under identical conditions.

Reaction of Pyridazine (1) with Methyl Radical (method B)

To a stirred solution of 1 (1.2g, 0.015mol) in 10% aq. H_2SO_4 (30ml) at 15°C (exp.3) or 25°C (exp.4), resp., t-BuOOH (4.05g, 0.045mol) and a saturated aq. solution of $FeSO_4 \cdot 7H_2O$ (12.5g, 0.045mol) were added dropwise simultaneously. After stirring for another 60 min the solution was basified with conc. NH_4OH and extracted with CH_2Cl_2. The solvent was removed in vacuo, the residue was analyzed by GLC (amine 220).

Identification of products: 1,2,3 were identified by comparison with authentic material.[16,17,18] Structure of 10 follows from GLC-ms [M^+ at m/e 136 (100%), major peaks at m/e 107, 93, 91, 77] and nmr data [2.60 (s, 6H, C-3-CH_3, C-6-CH_3), 2.23 (s, 6H, C-4-CH_3, C-5-CH_3)]. 8 and 9 were identified as trimethylpyridazines by means of ms-data [8: M^+ at m/e 122 (100%), major peaks at m/e 93, 79, 77; 9: M^+ at m/e 122 (100%), major peaks at m/e 93, 79, 77]. Differentiation between 8 and 9 was based on nmr data of the reaction mixture obtained from exp.2 (cf. Table 1). Besides signals of 10, the spectrum exhibits signals at 8.79 (s, 1H, H-6), 2.64 (s, 3H, C-3-CH_3), 2.27, 2.23 (2 x s, 2 x 3H, C-4-CH_3 and C-5-CH_3),[6] indicating the second main component of the mixture to be 8. On basis of molecular weights determined by ms, 4,5,6,7 were shown to be dimethylpyridazines. As the peak of one of these compounds exclusively appears in gaschromatograms of reaction mixtures obtained from 1 or 3 this product is assumed to be 4,5-dimethylpyridazine (7) [M^+ at m/e 108 (100%), major peaks at m/e 79, 77]. For another two dimethylpyridazines structures 4 and 5 had to be assigned, as these compounds could be detected by GLC as reaction products of 1 and 3 as well as 2, therefore obviously bearing methyl groups at α- and ß-positions. Accordingly the nmr spectrum of a mixture of these

two compounds separated from other reaction products by micropreparative GLC, exhibits signals of 3,4-dimethylpyridazine (4) [8.94 (d, J=5, 1H, H-6), 7.22 (d, J=5, 1H, H-5), 2.70 (s, 3H, C-3-CH_3), 2.33 (s, 3H, C-4-CH_3)] and 3,5-dimethylpyridazine (5) [8.90 (s, 1H, H-6), 7.18 (s, 1H, H-4), 2.70 (s, 3H, C-3-CH_3), 2.33 (s, 3H, C-4-CH_3)]. Mass spectra of 4 and 5 show almost identical fragmentation patterns[M^+ at m/e 108 (100%), major peaks at 79, 77)], however considering the intensity ratio of nmr signals permits assignement of compounds 4 and 5 to peaks in gas chromatograms. The dimethylated pyridazine, obtained from exps.1,3,4 (cf. Table 1) in <1% yield finally had to be 3,6-dimethylpyridazine (6) [M^+ at m/e 108, major peaks at m/e 107, 91, 79 (100%), 77)].

Reaction of Ethyl 4-pyridazinecarboxylate (11) with Methyl Radical

To a solution of 11[23] (2.28g, 0.015mol) in 10% aq. H_2SO_4 (30ml), equimolar amounts (cf. Table 3, exps.5,7) of t-BuOOH and $FeSO_4 \cdot 7H_2O$ (saturated aq. solution) were added dropwise simultaneously with stirring and cooling (20-25°C). The solution was stirred for another 60 min and then extracted with CH_2Cl_2. After removal of solvent the residue was analyzed by GLC (OV 17).

Repeated methylation (cf. Table 3, exp.6) was carried out under identical conditions. Ethyl 5-methyl-4-pyridazinecarboxylate (12): The nmr spectrum of the reaction mixture resulting from exp.5, containing 12 as main component, shows major peaks at 9.44 (s, 1H, H-3), 9.18 (s, 1H, H-6), 4.45 (q, J=7, 2H, CH_2), 2.63 (s, 3H, C-5-CH_3), 1.42 (t, J=7, 3H, CH_2-$\underline{CH_3}$).

(E)-Ethyl 5-styryl-4-pyridazinecarboxylate (13)

The mixture obtained from exp.5 (0.7g), benzaldehyde (1.06g, 0.01mol), pyridine (1.58g, 0.02mol) and piperidine (0.1g, 0.001mol) is stirred with heating (80°C) under nitrogen until conversion of 12 is complete (GLC: OV 17; ca. 48 h). After removal of volatile compounds by heating (70°C, 10^{-1}mbar) in a kugelrohr apparatus, the residue is crystallized from toluene yielding 0.4g (32%, based on 11) yellow crystals, mp 115-117°C. Ms: M^+ at m/e 254; ir: 1705 ($\nu_{C=O}$), 1618 ($\nu_{C=C}$), 970 (δ_{C-H}); nmr: 9.62 (s, 1H, H-3), 9.52 (s, 1H, H-6), 8.14, 7.96 (part of AB-system, J=18, 1H, -CH=), 7.74-7.30 (m, 6H, phenyl-H, -CH=), 4.48 (q, J=7, 2H, CH_2), 1.48 (t, J=7, 3H, CH_3); Anal. calcd. for $C_{15}H_{14}N_2O_2$: C, 70.91; H, 5.55; N, 11.02. Found: C, 70.78; H, 5.62; N, 10.93.

(E)-Ethyl 5-(2,4-dichlorostyryl)-4-pyridazinecarboxylate (14)

14 is prepared according to the method above starting with 2,4-dichlorobenzaldehyde. Crystallisation from toluene yields 0.5 g (34% based on 11) of yellow crystals, mp 102-104°C. Ms: M^+ at m/e 322 (100%), 324 (68%), 326 (11%); ir: 1725 ($\nu_{C=O}$), 1620 ($\nu_{C=C}$), 960 (δ_{C-H}); nmr: 9.56 (s, 1H, H-3), 9.47 (s, 1H, H-6), 8.07-7.18 (m, 5H, phenyl-H, 2 x -CH=), 4.45 (q, J=7, 2H, CH_2), 1.43 (t, J=7, 3H, CH_3); Anal. calcd. for $C_{15}H_{12}N_2O_2Cl_2$: C, 55.74; H, 3.74; N, 8.67. Found: C, 55.74; H, 3.84; N, 8.68.

ACKNOWLEDGEMENTS

We are grateful to the "Hochschuljubiläumsstiftung der Stadt Wien" for financial support and to B. Kiener and G. Zinsberger for skillful technical assistance.

REFERENCES AND NOTES

1. XIX: G. Allmaier and G. Heinisch, J. Heterocyclic Chem., in press
2. F. Minisci, Synthesis, 1973, 1; F. Minisci and O. Porta, Advan. Heterocycl. Chem., 1974, 123; F. Minisci, Topics Curr. Chem., 1976, 62, 1
3. A. Pollak, B. Stanovnik and M. Tišler, Tetrahedron, 1968, 2623
4. M. Japelj, B. Stanovnik and M. Tišler, Monatsh. Chem., 1969, 100, 671
5. F. Minisci, R. Bernardi, F. Bertini, R. Galli and M. Perchinummo, Tetrahedron, 1971, 3575
6. T. Tsuchiya, H. Arai and H. Igeta, Chem. Pharm. Bull., 1972, 20, 273
7. A. Jentzsch, Ph. D. thesis, University of Vienna, 1974
8. G. Heinisch, A. Jentzsch and M. Pailer, Monatsh. Chem., 1974, 105, 648
9. M. Braun, G. Hanel and G. Heinisch, Monatsh. Chem., 1978, 109, 63
10. G. Heinisch, A. Jentzsch and I. Kirchner, Tetrahedron Lett., 1978, 619
11. G. Heinisch and I. Kirchner, Monatsh. Chem., 1979, 110, 365
12. G. Heinisch and I. Kirchner, J. Heterocycl. Chem., 1980, 17, 1501
13. G. Heinisch, I. Kirchner, I. Kurzmann, G. Lötsch and R. Waglechner, Arch. Pharm. (Weinheim), 1983, 316, 508
14. F. Minisci, R. Galli, V. Malatesta and T. Caronna, Tetrahedron, 1970, 4083
15. By changing the rate of addition of persulphate there is neither considerable difference in conversion rate nor in ratio of products.
16. R. Mizzoni and P. Spoerri, J. Am. Chem. Soc., 1951, 73, 1873

17. O. Poppenberg, Chem. Ber., 1901, 34, 3257

18. R. Mizzoni and P. Spoerri, J. Am. Chem. Soc., 1954, 76, 2201

19. R. Horning and E. Amstutz, J. Org. Chem., 1955, 20, 707

20. J. Levisalles, Bull. Soc. Chim. France, 1957, 1004

21. J. Levisalles and P. Baranger, Compt. Rend., 1956, 242, 1336

22. J. Bradshaw, M. Tišler and B. Stanovnik, J. Org. Chem., 1974, 39, 793

23. W. Leanza, H. Becker and E. Rogers, J. Am. Chem. Soc., 1953, 75, 4086

Received, 13th February, 1984