Tetrahedron Letters, Vol. 34, No. 24, pp. 3903-3906, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

A New Two-Step Procedure for Functionalized-3(2H)-Pyridazinones through Homolytic Substitution of 3-Chloropyridazines.[1]

Vittorio Dal Piaz*, Maria Paola Giovannoni and Giovanna Ciciani

Dipartimento di Scienze Farmaceutiche dell'Università, Via Gino Capponi, 9, I-50121, Firenze, Italy

Abstract: *The homolytic substitution of protonated 3-chloro-6-methylpyridazine* ***1a****, followed by hydrolysis with AcOH affords 4- or 4,5-functionalized pyridazinones* ***3a-c****. Less reactivity is found for 3-chloro-6-phenylpyridazine* ***1b****. Hypotheses about these different behaviour patterns are proposed and discussed.*

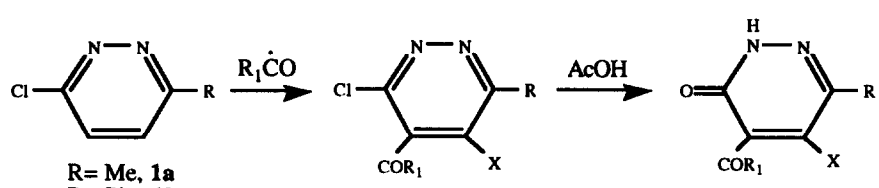
Owing to their application in agriculture as herbicides[2] and in medicine as antihypertensives, platelet aggregation inhibitors and cardiotonics,[3] 3(2H)-pyridazinones have aroused great interest in recent years. The introduction of functional groups into this system allows modulation of the biological activity of unsubstituted or alkyl substituted pharmacologically-active compounds.[4,5] On the other hand functionalized pyridazinones are also useful as synthetic building blocks for a variety of fused pyridazines.[6-9]

Previous papers from our laboratory[10-13] have dealt with the synthesis of various 4,5-functionalized pyridazinones by the reductive or oxidative ring opening of isoxazolopyridazinones. We now report a new experimentally simple two-step procedure for other kinds of functionalized pyridazinones, starting from the easily available precursors **1a,b**.

The homolytic substitution (Minisci-type reaction) of protonated 3-chloro-6-methylpyridazine **1a** with redox-generated COMe, COPh and COOEt nucleophilic radicals affords **2a-c**; on the other hand the same reactions performed on 3-chloro-6-phenylpyridazine **1b** allowed us to obtain only the 4-acetyl-3-chloro-6-phenylpyridazine **2d**. From the reactions of **1b** with COPh and COOEt radicals we recovered the starting material unchanged, though we varied the initiator and the reaction conditions.

Conversion of **2a-d** into the corresponding pyridazinones **3a-d** occurs rapidly and in nearly quantitative yield upon treatment with AcOH (Scheme 1, Table 1).[14]

Scheme 1



R= Me, **1a**
R= Ph, **1b**

2a-d **3a-d**

R_1= Me, Ph, EtO

2-3	R	R_1	X
a	Me	Me	H
b	Me	Ph	H
c	Me	OEt	COOEt
d	Ph	Me	H

In agreement with data from previous experiments performed in the 1,2-diazine system, first by Heinisch[15], and then by Samaritoni[16], our reactions demonstrated good regioselectivity for the 4-position. The same type of regioselectivity probably occurs in the reaction between **1a** and COOEt radical, but it is impossible to verify, because the first-introduced COOEt group activates the 1,2-diazine system for attack by another radical, leading to the formation of diethyl 3-chloro-6-methylpyridazine-4,5-carboxylate **2c**.[17] In these reactions we observed low conversion rates; in fact generally 18-25% of the unreacted **1** can be recovered from the reaction mixtures.

Table 1. New functionalized 3-chloropyridazines **2a-d** and pyridazinones **3a-d**

substrate	product	initiator	conversion %	yield* %	m.p. (C°)	substrate	product	yield %	m.p. (C°)
1a	**2a**	H_2O_2	75	37	oil**	**2a**	**3a**	97	206-208
1a	**2b**	t-BuOOH	82	22	97-99	**2b**	**3b**	95	177-179
1a	**2c**	H_2O_2	100	48	oil**	**2c**	**3c**	93	112-114
1b	**2d**	t-BuOOH	82	24	92-94	**2d**	**3d**	92	>300

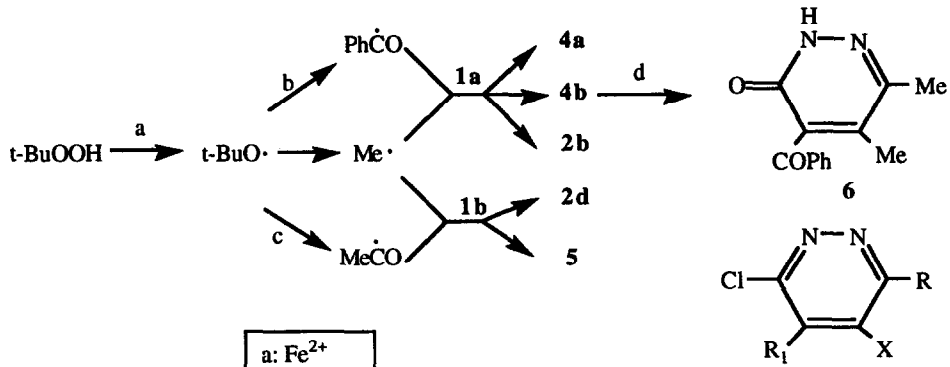
* yield based on converted **1a** and **1b**. ** purified by column chromatography.
General procedure:
A) To a stirred mixture of **1a** or **1b** (1mmole), 3% H_2SO_4 (6ml), acetone or acetonitrile (3-5 ml) and the radical precursor (MeCHO or PhCHO for MeCO and PhCO radical, respectively, 20 mmoles), t-BuOOH or 34% H_2O_2 (20 mmoles) and a saturated solution of $FeSO_4$ (20 mmoles) were added simultaneously and separately at r.t., over a 10-minute period. The temperature rose to 30-35 °C; after 5 minutes the mixture, cooled and diluted with water was basified with 20% Na_2CO_3 and exhaustively extracted with CH_2Cl_2. Evaporation in vacuo afforded a residue which was chromatographed. **2c** Was prepared using the same molar ratios, adding a cooled (-5°C) mixture of H_2O_2 and ethylpyruvate to a stirred and cooled mixture of **1a**, 3% H_2SO_4 and $FeSO_4$.
B) 0.25 Mmoles of **2a-d** were refluxed with AcOH (4 ml) for 2-8 hours. Evaporation in vacuo afforded the almost pure pyridazinones **3a-d**.

The difference in reactivity between **1a** and **1b** towards COPh radical cannot be explained in terms of the weaker electrophilicity of **1b** because in this compound the proton linked to the 4-carbon is more deshielded than the same hydrogen of **1a** (7.82 versus 7.40). Moreover, from the sequence of nucleophilicity (Me<p-alkyl<COMe<COPh<s-alkyl<t-alkyl) inferred by Minisci [18] from the homolytic substitution of pyridines and quinolines, it emerges that COPh radical is more nucleophilic and therefore presumably more reactive than the COMe radical. On the other hand steric grounds can also be excluded because **1b**, as reported by Samaritoni,[16] is easily alkylated by the highly nucleophilic and bulky t-butyl radical, as well as by the weakly nucleophilic ethyl radical. In experiments performed with t-BuOOH as initiator of the reactions, we observed for both substrates a strong competition between the acyl (aroyl) radical arising from the aldheydes and the methyl radical (the least nucleophilic in Minisci's scale) originating from the decomposition of the peroxide.[19] Thus the products **4a** , **5**[20] and **4b**[21] were also obtained from the reaction mixtures; hydrolysis of **4b** with AcOH afforded **6**[21] (Scheme 2).

Similar competitive reactions, never described by Minisci in the homolytic acylation of pyridines and quinolines, suggest that a different scale of nucleophilicity or, more probably, a different reaction mechanism

might operate in the homolytic acylation of pyridazines. In the latter polar factors probably play a less important role then in other heteroaromatic bases. Results obtained by Ostrowicz[22], in the vicarious nucleophilic substitution (VNS) of pyridazine and 3-chloropyridazine seem to comfirm this hypothesis. In fact the first compound, which easily undergoes homolytic substitution at 4-position by a variety of nucleophilic radicals[15], is unreactive in VNS, whereas the introduction of a chlorine group, which promotes the VNS at the neighbouring position, reduces the reactivity in homolytic substitution, as observed by us for **1b**.

Scheme 2



Comp.	R	R_1	X	yield %
4a	Me	Me	H	15
4b	Me	COPh	Me	48
5	Ph	Me	H	21
2b				18
2d				19

Our results and our hypothesis agree with data from previous investigations, which demonstrated that a marked difference in homolytic substitution between pyridazines and other π-deficent heteroaromatic bases exists, not only with respect to site-selectivity, but also because in the 1,2-diazine system the β-positions are also attacked by non-nucleophilic radicals, whereas the positions of lowest electron density (C3,C6) are almost completely unaffected.[15] On the basis of these data the weaker nucleophilicity of ·COOEt as compared to the acetyl radical[23] cannot be used to explain the absence of reactivity of **1b** with the ethoxycarbonyl radical.

In conclusion our method, due to the availability of synthetic precursors, and the experimentally simple procedure may have some utility for preparing functionalized pyridazinones of type **3a-d**. Moreover the obtained results provide further evidence of the unusual reactivity of pyridazines.

Further studies are in progress in order to clarify the role played by the phenyl in 6-position on the reactivity of pyridazines of type **1b**.

Acknowledgments: we thank the MURST and CNR for financial support.

References and Notes

1. Part of this work was presented, as a lecture, at the "*3rd International Symposium on the Chemistry and Pharmacology of Pyridazines*"; September 9-11, **1992,** Como (Italy).
2. Schober B. D., Megyeri G., Kappe T., *J. Heterocyclic Chem.*, **1989**, 26, 169 and references therein cited.
3. Heinisch G., Frank H., "Pharmacologically active Pyridazine derivatives". Part 1, in "*Progress in Medicinal Chemistry*", vol. 27, ed. Ellis G. P., West G. B., **1990**, 1; ibidem, Heinisch G., Frank H., Part 2, vol. 29, **1992**, 142.
4. Wermuth C. G., Schlewer G., Bourguignon J. J., Maghioros G., Bouchet M. G., Moire C., Kan G. P., Worms P., Biziere K., *J. Med Chem.*, **1989**, 32, 528.
5. Badger E. V., Moos W. H., *J. Heterocyclic Chem.*, **1986**, 23, 1515.
6. Haider N., Heinisch G., *J. Chem. Soc. Perkin Trans. I*, **1986**, 169 and references therein cited.
7. Dal Piaz V., Ciciani G., Giovannoni M. P., Turco G., *Heterocycles*, **1989**, 29, 1595.
8. Gozlan S. A. S., Mohamed M. H., Fakhr Y., Elnagdi M. H., *Liebigs Ann. Chem.*, **1990**, 293.
9. Khalifa F. A., *Arch. Pharm.*, **1990**, 323, 883.
10. Dal Piaz V., Ciciani G., Turco G., *Synthesis*, **1989**, 213.
11. Dal Piaz V., Ciciani G., Giovannoni M. P., *Heterocycles*, **1991**, 32, 1173.
12. Dal Piaz V., Ciciani G., Giovannoni M. P., *Tetrahedron Letters*, **1991**, 27, 3229.
13. Dal Piaz V., Ciciani G., Turco G., Giovannoni M. P., Miceli M., Pirisino R., Perretti M., *J. Pharm. Sci.*, **1991**, 80, 341.
14. The structure of compounds **2a,b** and **2d** is also based on the following evidence: hydrolysis of **2d** affords **3d** which was methylated to give the 2-methyl derivative, isomeric with 5-acetyl-2-methyl-6-phenyl-3(2H)-pyridazinone[13] as proven on the basis of m.p., ir and nmr spectra; proton resonance values of **2a,b** agree with that of **2d** (200 MHz, $CDCl_3$, δ= 2.75: s, 3H, $COCH_3$; δ= 7.55: m, 3H, Ar; δ=7.90: s, 1H, 5-Py; δ= 8.10: m, 2H, Ar).
15. Heinisch G., *Heterocycles*, **1987**, 26, 481 and references therein cited.
16. Samaritoni J. G., Babbitt G., *J. Heterocyclic Chem.*, **1991**, 28, 583 and references therein cited.
17. Attempts to introduce only one COOEt group into 4-position, using base: peroxide ratio 3:1 in a two-phase system, following reference 15, were unsuccessful.
18. Caronna T., Fronza G., Minisci F., Porta O., Gardini G. P., *J. Chem. Soc. Perkin II*, **1972**, 1477.
19. Reactions carried out on **1a** in the absence of aldehyde, leading to **4a** as a sole product, confirm this hypothesis; also from the reaction of **1a** with the COMe radical in presence of t-BuOOH, only **4a** is obtained.
20. These compounds have already been described: **4a**: Becker H. G., Bottcher H., *Tetrahedron*, **1968**, 24, 2687. **5**: Albright J. D., Mc Evoy F. J., Moran D. B., *J. Heterocyclic Chem.*, **1978**, 15, 881.
21. **4b**, m.p. 130-131°C; **6** m.p. 206-208°C (93% yield).
22. Ostrowicz A., Baloniak S., Makosza M., Rykowsky A., *Tetrahedron Letters*, **1992**, 33, 4787.
23. Bernardi R., Caronna T., Galli R., Minisci F., Perchinunno M., *Tetrahedron Letters*, **1973**, 9, 645.

All new compounds display satisfactory spectroscopic (IR, 1H-NMR) and analytical (C, H, N) data.

(Received in UK 15 April 1993)