IMIDAZOLE DERIVATIVES. PART V.[1]
IMIDAZO[1′,2′:1,6]PYRIDO[2,3-*d*]PYRIDAZINE: SYNTHESIS, STRUCTURE, AND PRELIMINARY CHEMISTRY OF A NOVEL HETEROCYCLIC RING SYSTEM

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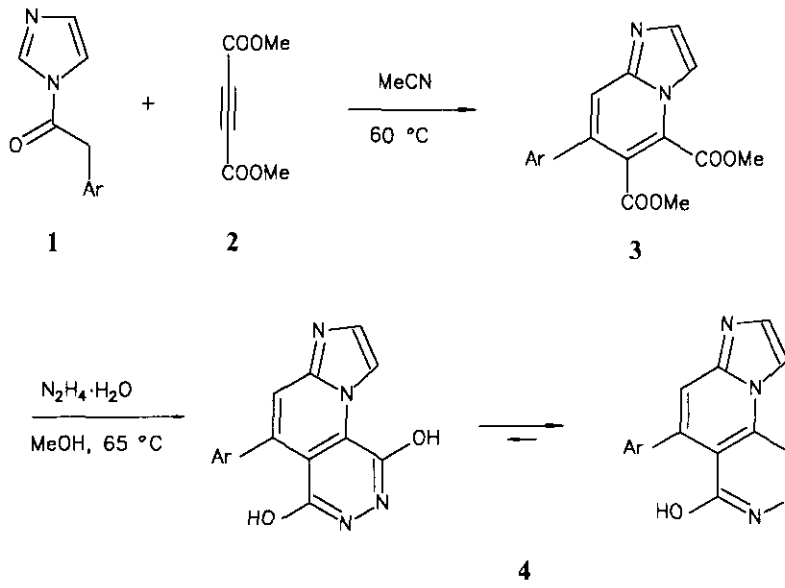
Abstract- Reaction of functionalized imidazo[1,2-*a*]pyridines with hydrazine hydrate to the novel imidazo[1′,2′:1,6]pyrido[2,3-*d*]pyridazine ring system is described.

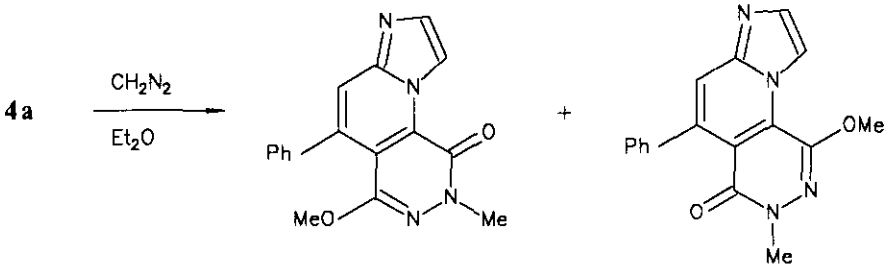
In the course of our studies of the transacylation reactions of acylated imidazole derivatives with activated alkynes[1-4] we recently found a simple one-pot procedure for the synthesis of imidazo[1,2-*a*]pyridines (**3**) by a novel condensation reaction of 1-(arylacetyl)imidazoles (**1**) with dimethyl acetylenedicarboxylate (**2**) (**3a**: 64%, **3b**: 89% yield)[2,3] (Scheme 1). We now investigated the utility of the obtained imidazo[1,2-*a*]pyridines (**3**) as precursors of novel tricyclic heteroaromatic ring systems containing a bridgehead nitrogen atom. The dimethyl 5,6-dicarboxylate moiety should be suitable in order to achieve annulations of further rings by reaction with appropriate 1,2-double donors. Herein we present a first application of such an annulation leading to the hitherto unknown imidazo[1′,2′:1,6]pyrido[2,3-*d*]pyridazine framework, which is confirmed by an X-ray analysis of one derivative, together with a preliminary study of the regioselective functionalization of the annulated pyridazine ring. Thus reaction of the imidazo[1,2-*a*]pyridines (**3**) with hydrazine hydrate in methanol under reflux provides the 5-arylimidazo[1′,2′:1,6]pyrido[2,3-*d*]pyridazine-1,4-diols (**4**) by simple crystallization in almost quantitative yields (**4a**: 97%, **4b**: 99% yield) (Scheme 1). The pyridazines (**4**) obtained by this convenient procedure are stable yellow compounds of high purity and exhibit a similar fluorescence as observed for the imidazo[1,2-*a*]pyridines (**3**) although at smaller wavelengths (data of compound **4a** in methanol, uv absorption maximum: 365 nm, fluorescence emission maximum: 459 nm).



a : Ar = C_6H_5 ; **b** : 4-$MeOC_6H_4$

Scheme 1.

It is known that the parent maleic hydrazide exists almost exclusively in the hydroxypyridazinone form.[5] From the four possible tautomers of the pyridazines (**4**) the 1-oxo-4-hydroxy form is favored (as depicted in Scheme 1) based on ^{1}H-nmr evidence (downfield shift observed for the 9-proton, **4a**: $\delta_{9\text{-H}}$=9.74 ppm in DMSO-d_6). However, the dimethylation of the pyridazine (**4a**) using diazomethane, which is known to afford the *N,O*-dimethyl derivative with maleic hydrazide,[5,6] gives an almost 1 : 1 mixture of the two possible regioisomers (**5**) and (**6**) along with only a trace of the di-*O*-methylated product (Scheme 2).



Scheme 2.

The structure assignment of the dimethyl derivatives (**5**) and (**6**) is based on the downfield shift of the 9-proton in the ^{1}H-nmr spectrum of **5** due to the deshielding caused by the neighboring carbonyl group (**5**: $\delta_{9\text{-H}}$=9.59 ppm, **6**: $\delta_{9\text{-H}}$=8.74 ppm, in $CDCl_3$). To confirm this assignment and to get more structural information about the novel heterocyclic ring system we determined the structure of compound (**5**) by X-ray analysis[7] (Figure 1).

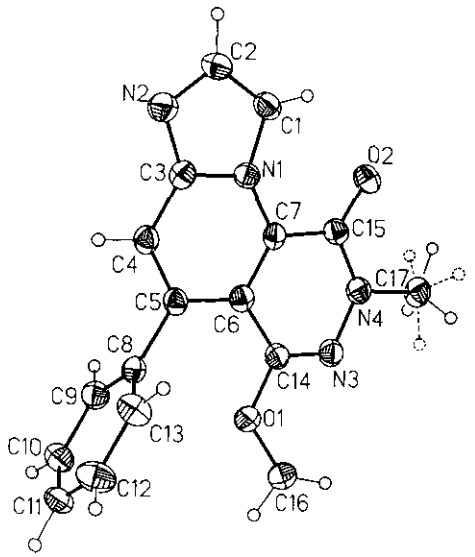
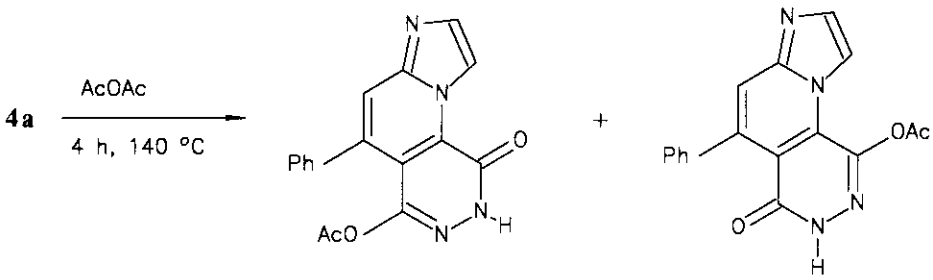


Figure 1.

The obtained molecular structure of the dimethyl derivative (**5**) is in agreement with the spectral data (^{1}H-nmr and ^{13}C-nmr) and supports the assignments of the regioselectivity of the tautomerization of the pyridazines (**4**) and of the dimethylation to (**5**) and (**6**), which both of them based mainly on nmr arguments (see above). It was found that the *N*-methyl group of compound (**5**) adopts two conformations in the crystal with the same probability, one with relatively close intramolecular O···H contacts of 2.29 **Å**.

Maleic hydrazide is reported to afford exclusively the mono-*O*-acetylated product on reflux in acetic anhydride.[8] We observed a 9 : 1 regioselectivity (76% yield) in favor of the 4-acetoxy derivative (**7**) by application of this method to the pyridazine (**4a**) (Scheme 3).

The possibility of regioselective functionalization of the pyridazine ring in the 5-arylimidazo[1′,2′:1,6]pyrido[2,3-*d*]pyridazine-1,4-diols (**4**) has been demonstrated. Further studies of chemo- and regioselective transformations of this novel heterocyclic framework, such as reductions and electrophilic aromatic substitutions, are in progress and will be reported in a forthcoming full paper.



7 8

ratio 9 : 1

Scheme 3.

ACKNOWLEDGEMENTS

This work was supported by the Deutsche Forschungsgemeinschaft. We thank Dr. V. Wray, Gesellschaft für Biotechnologische Forschung (GBF), Braunschweig-Stöckheim, for recording the ^{13}C-nmr spectra and Dr. F. Sasse, GBF, for the fluorescence spectra.

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7. **5**: monoclinic, space group $P2_1/c$, a = 11.200(2), b = 15.958(3), c = 8.559(2) Å, $\alpha = \gamma = 90°$, $\beta = 111.88(1)°$, V = 1419.3(5) Å^3, Z = 4, $\rho_{calcd} = 1.429$ g cm^{-3}, $\mu = 0.9$ cm^{-1}, T = 155 K, $Mo_{K\alpha}$ radiation (graphite monochromator), scan range $3° \leq 2\theta \leq 45°$, independent reflections 1865, observed 1465 ($F_o \geq 4\sigma(F)$), R = 0.049, $R_w = 0.055$. Further details of the crystal structure investigation may be obtained from the Fachinformationszentrum Karlsruhe, Gesellschaft für wissenschaftlich-technische Information mbH, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD-320124, the names of the authors and the journal citation.
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Received, 4th June, 1990