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Imidazole Derivatives, Part IX[1]

Selective Reactions of Functionalized Imidazo[1,2-a]pyridines: Stereospecific Synthesis of 5,6-Dihydroimidazo[1,2-a]pyridines

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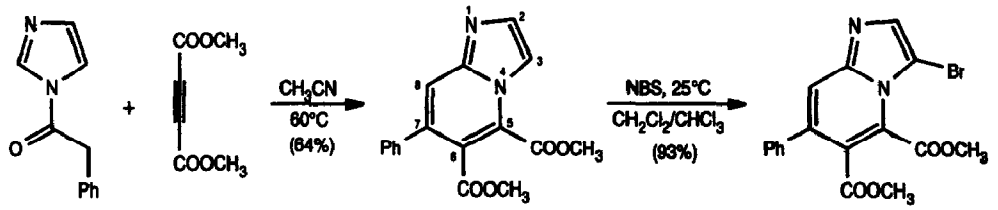
Abstract: Chemo-, regio-, and stereoselective reactions of the 5,6-dimethoxycarbonyl-functionalized imidazo[1,2-a]pyridine **3** provide various derivatives including the novel furo[3,4-e]imidazo[1,2-a]pyridine and cyclopropa[e]imidazo[1,2-a]pyridine ring systems.

Imidazo[1,2-a]pyridine derivatives have attracted increasing interest over the past years[2] because of their useful biological activities (*e.g.* antifungal, anthelmintic, antibacterial, and local anesthetic activity[3]). Most striking are the gastric antisecretory and cytoprotective properties which have been reported for a series of substituted imidazo[1,2-a]pyridines.[4] The gastric antisecretory activity is ascribed to a selective inhibition of the H^+/K^+-ATPase enzyme.[5] This mechanism of action suggests that these compounds are potential novel antiulcer agents.

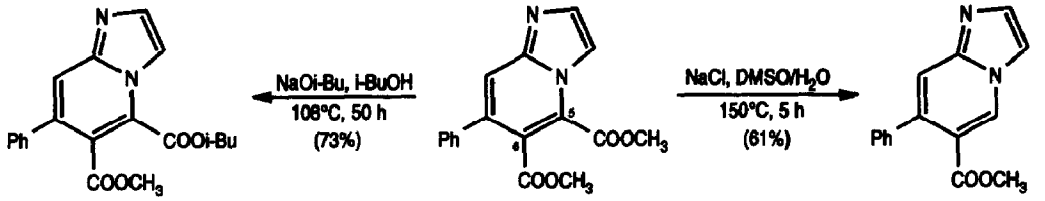
We described a novel synthesis of functionalized imidazo[1,2-a]pyridines by the unprecedented imidazolide-DMAD condensation reaction.[6,7] Treatment of 1-phenylacetylimidazole **1** with dimethyl acetylenedicarboxylate (DMAD) **2** in acetonitrile at 60°C afforded the imidazo[1,2-a]pyridine **3** in 64% yield (Scheme 1). The imidazo[1,2-a]pyridines **3** are also of interest because of their physical properties. They show an intense fluorescence in the visible region with remarkably large Stokes shifts even in the crystalline state.[7] Herein we describe highly regio-, chemo-, and stereoselective transformations of compound **3** providing novel substituted imidazo[1,2-a]pyridines.



Scheme 1

We reported previously that 4,5-substituted imidazolides undergo the imidazolide-DMAD condensation reaction leading to 2,3-substituted imidazo[1,2-a]pyridines. However, the yields in these cases were considerably lower (12 to 47%).[7] Therefore, we envisaged to get access to 3-substituted imidazo[1,2-a]pyridines *via* electrophilic aromatic substitution of compound **3**. Electrophilic substitution of imidazo[1,2-a]pyridines, which represent a 10 π-electron heteroaromatic system with a bridgehead nitrogen atom, was previously shown to proceed regioselectively in the 3-position.[8] In fact, bromination of **3** with NBS regioselectively gave the 3-bromo derivative **4** in 93% yield (Scheme 1).[9] By this procedure selective functionalization of the imidazole ring becomes possible and introduction of further groups should be feasible by palladium-catalyzed coupling reactions.

The imidazo[1,2-a]pyridines resulting from the imidazole-DMAD condensation reaction have a methoxycarbonyl substituent in the 5- and in the 6-position. Our next goal was to achieve a chemoselective differentiation between these two groups. We viewed the 6-methoxycarbonyl group as part of a vinylogous urethane system, which therefore should be decreased in its reactivity towards nucleophilic attack. Moreover, selective reactions at the ester group in the 5-position should also be favored for steric reasons. Thus, reactions initiated by nucleophilic addition at the carbonyl group of the ester moiety were expected to occur regioselectively at the 5-methoxycarbonyl function.



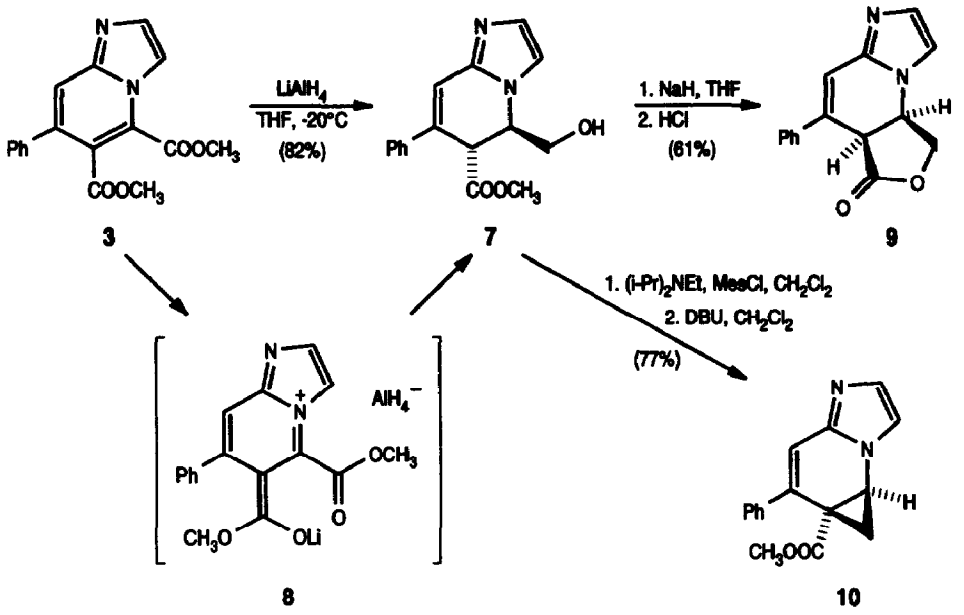
Scheme 2

This hypothesis was proven by refluxing the imidazo[1,2-a]pyridine **3** in sodium *iso*-butanolate/*iso*-butanol. Transesterification took place exclusively at the 5-methylester and afforded the 5-*iso*-butoxycarbonyl compound **5** (Scheme 2). The structural assignment is based on the ^{1}H-NMR spectrum.[9] The signal for the 5-methylester of the imidazo[1,2-a]pyridine **3** appears at 4.03 ppm and for the 6-methylester at 3.65 ppm.[7] Compound **5** shows a singlet for the 6-methylester at 3.60 ppm. This assignment has been additionally confirmed by NOE experiments.

The Krapcho demethoxycarbonylation procedure[10] was applied to the imidazo[1,2-a]pyridine **3**, and regioselectively provided the 6-methoxycarbonyl derivative **6**. The singlet for the 6-methylester in the ^{1}H-NMR spectrum of **6** appears at 3.68 ppm and the 5-H at 8.82 ppm as a doublet ($J_{5,8}$ = 0.75 Hz).[9] Additional confirmation for this regioselectivity has been obtained from NOE experiments.

Reduction of **3** with lithium aluminum hydride regio- and stereoselectively provided the 5-hydroxymethyl derivative **7** (Scheme 3). Surprisingly, the 6-methoxycarbonyl group was not affected even when using a large excess of the reducing agent, but the aromatic 5,6-double bond was reduced and the 5,6-*trans*-substituted compound **7** was obtained stereoselectively. The structure assignment for **7** is based on the

^{1}H-NMR data.[9] The coupling constant between the 5-H at 4.77 ppm and 6-H at 4.32 ppm is J = 1.1 Hz, which is characteristic of a *trans* arrangement. Extensive NOE studies at **7** confirmed this stereochemical assignment. The selective formation of **7** is rationalized by formation of intermediate **8**. Finally, reduction of the iminium cation regenerates the aromatic imidazole system and reduction of the 5-methylester followed by protonation of the ester enolate during workup affords the thermodynamically favored *trans* isomer.



Scheme 3

Further support for the stereochemistry of **7** was obtained by the spontaneous lactonization to **9** after epimerization at C-6. The coupling constant between the 5-H at 5.18 ppm and the 6-H at 4.78 ppm in the ^{1}H-NMR spectrum of **9** is J = 6.6 Hz.[9] Transformation of **7** into the corresponding mesylate and subsequent treatment with DBU provided the cyclopropane **10**. Structural assignment for **10** is supported by the ^{1}H-NMR data (cyclopropane protons at 0.96, 2.53, and 4.11 ppm with characteristic couplings) and is in agreement with NOE experiments.[9] The formation of the three-membered ring of **10** is explained in terms of a base-initiated 1,3-elimination which proceeds presumably *via* a W-shaped transition state.[11,12]

The furo[3,4-e]imidazo[1,2-a]pyridine framework of **9** and the cyclopropa[e]imidazo[1,2-a]pyridine framework of **10** represent novel heterocyclic ring systems. We have noted earlier that the imidazo[1,2-a]pyridine **3** is a useful synthon for building novel nitrogen heterocycles.[13] The synthesis of the hitherto unprecedented skeletons **9** and **10** provides further examples.

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9. ^{1}H-NMR data (200 MHz) of the functionalized imidazo[1,2-a]pyridines **4**, **5**, **6**, **7**, **9**, **10** (*J* in Hz). **4** ($CDCl_3$): δ 3.60 (s, 3 H), 4.06 (s, 3 H), 7.33-7.45 (m, 5 H), 7.69 (s, 1 H), 7.74 (s, 1 H). **5** ($CDCl_3$): δ 1.02 (d, *J* = 6.7, 6 H), 2.08 (non, *J* = 6.7, 1 H), 3.60 (s, 3 H), 4.23 (d, *J* = 6.7, 2 H), 7.36-7.46 (m, 5 H), 7.83 (d, *J* = 0.7, 1 H), 7.84 (d, *J* = 1.3, 1 H), 8.51 (dd, *J* = 1.3, 0.7, 1 H). **6** ($CDCl_3$): δ 3.68 (s, 3 H), 7.31-7.43 (m, 5 H), 7.56 (t, *J* = 0.75, 1 H), 7.67 (dd, *J* = 1.3, 0.75, 1 H), 7.73 (d, *J* = 1.3, 1 H), 8.82 (d, *J* = 0.75, 1 H). **7** (CD_3SOCD_3): δ 3.31-3.49 (m, 2 H), 3.55 (s, 3 H), 4.32 (d, *J* = 1.1, 1 H), 4.77 (dt, *J* = 1.1, 8.0, 1 H), 5.41 (t, *J* = 5.4, 1 H), 6.96 (d, *J* = 1.1, 1 H), 7.07 (s, 1 H), 7.26 (d, *J* = 0.8, 1 H), 7.33-7.46 (m, 3 H), 7.62-7.67 (m, 2 H). **9** (CD_3SOCD_3): δ 4.77 (dd, *J* = 10.5, 3.5, 1 H), 4.78 (d, *J* = 6.6, 1 H), 5.01 (d, *J* = 10.5, 1 H), 5.18 (dd, *J* = 6.6, 3.5, 1 H), 7.13 (br s, 1 H), 7.16 (br s, 1 H), 7.36-7.49 (m, 3 H), 7.54 (br s, 1 H), 7.74-7.78 (m, 2 H). **10** ($CDCl_3$): δ 0.96 (t, *J* = 5.3, 1 H), 2.53 (dd, *J* = 7.8, 5.4, 1 H), 3.46 (s, 3 H), 4.11 (dd, *J* = 7.8, 5.3, 1 H), 6.81 (d, *J* = 0.6, 1 H), 7.13 (dd, *J* = 1.2, 0.6, 1 H), 7.18 (d, *J* = 1.2, 1 H), 7.33-7.56 (m, 5 H).
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