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Multicomponent assembling of imidazole *N*-oxides, aldehydes and CH-acids: A simple and efficient approach to newly functionalized imidazole derivatives

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ABSTRACT

An efficient and simple method for C2-functionalization of 2-unsubstituted imidazole *N*-oxides has been developed. It consists at the condensation of 2-unsubstituted imidazole *N*-oxides with aldehydes and CH-acids. This method permits broad variations in the structure of starting materials.

1. Introduction

Imidazole *N*-oxides are interesting compounds due to their applications as building blocks in advanced heterocyclic chemistry,[1,2] natural product synthesis, coordination chemistry,[3] and catalysis.[4] In addition, imidazole derivatives play a significant role in various biochemical processes and exhibit a diverse scope of biological activities.[5,6] The imidazole core is present in many natural compounds such as histidine and the related hormone histamine.

In this context, development of new effective methods for the synthesis of imidazole derivatives is therefore of great importance. There are two fundamentally different approaches for their synthesis. The first way involves preparation of imidazoles from acyclic precursors using various cyclocondensation reactions.[7] The second way entails direct C-H functionalization of the imidazole ring using mostly transition metal-catalyzed reactions. It is known that the *N*-oxide group imparts a great increase in reactivity in reactions with electrophilic reagents at all positions, and especially at the C2-position, it allows efficient regioselective C2-functionalization. However, C2-functionalization of imidazole *N*-oxides with preservation of the *N*-oxide group is known only in case of using transition metal catalysis.[8] Examples of functionalization without catalysis are mostly accompanied by deoxygenation.[9]

In our earlier work we have described C2-functionalization of 1-benzyl-4,5-dimethylimidazole *N*-oxide via condensation with aldehydes and Meldrum's acid proceeding under mild conditions.[10] In the present study, we have expanded this reaction to the broad scope of CH-acids and imidazole *N*-oxides.

2. Results and discussion

It was found that 2-unsubstituted imidazole *N*-oxides **1** reacts with various CH-acids **2** and aldehydes **3** with the formation of products **4a-w** (Table 1).

Various 2-unsubstituted 1-alkyl-4,5-dimethylimidazole *N*-oxides (**1a-f**), 1-arylimidazole *N*-oxide **1g** and 1-alkyl-2,4-

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unsubstituted **1h** and various aldehydes, including aromatic (**2a,b**), heteroaromatic (**2c-e**), aliphatic (**2f**) and formaldehyde (as 37% water solution) were selected. CH-acids were represented by barbituric acid **3a**, 1,3-dimethylbarbituric acid **3b**, dimedone **3c**, 1,3-indandione **3d**, 4-hydroxy-6-methyl-2H-pyran-2-one **3e** and 4-hydroxycoumarin **3f**. Assembling various combinations of these building blocks, we were able to prepare a library of functionalized imidazole derivatives. It should be noted that in case of *N*-oxide **1h** which has two available positions, only the product of reaction on position C2 was obtained (**4o**).

The yields of the discussed condensation are practically independent of nature of both the imidazole *N*-oxide and the CH-acid, but are determined by the ease of the pure product isolation (Table 1).

Most probably, the reaction begins with nucleophilic addition of CH-acid to the aldehyde with the formation of the corresponding enone, followed by the Michael-type addition of imidazole *N*-oxide (Scheme 1).

In addition, it is necessary to note that in this three-component reaction product can be obtained even in the case of using CH-acids such as 4-hydroxycoumarin and 4-hydroxy-6-methylpyrone, which are known not to form stable enones in reaction with aldehydes.[11]

In the case of using thiazolidine-2,4-dione **5** as CH-acid, the reaction stops at the formation of enone **6**, which can be isolated from the reaction mixture. This fact can be explained by the lack of activity of this enone as a Michael acceptor. Attempts to use acyclic β-dicarbonyl compounds such as acetylacetone **5a**, diethylmalonate **5b** and ethyl acetoacetate **5c** also failed. Most probably corresponding enones do not form under the reaction conditions (Scheme 2) and only the starting *N*-oxide **1b** was isolated from the reaction mixture.

The molecular structures of **4a-w** were established by ^{1}H and ^{13}C NMR spectrometry and HRMS. The ^{1}H NMR spectra of all compounds **4** displayed a very characteristic singlet at 16–18 ppm for the N-OH proton. Similar signals can also be observed in ^{1}H NMR spectra of products of condensation of 1-benzyl-4,5-dimethylimidazole *N*-oxide with aldehydes and Meldrum's acid which were reported in our earlier work.[10]

Imidazole *N*-oxides were obtained in analogy to the already described procedures. 1,3,5-Triazinanes **9a-b** were obtained by treatment of the corresponding amines **8** with paraformaldehyde in methanol at room temperature. The crude products were used for the further reaction with butane-2,3-dione monooxime **11** in refluxing EtOH without purification. Under these conditions, triazines are known to undergo dissociation, and the monomeric formaldehyde imines (*N*-methyleneamines) reacts with **11** to give imidazole *N*-oxides **1e**,**f**. Imidazole *N*-oxides **1g**,**h** were prepared as shown in the scheme below (Scheme 3).

3. Conclusion

In conclusion, we described the new condensation of 2-unsubstituted imidazole *N*-oxides with aldehydes and CH-acids. The described procedure is operationally simple and chromatography free. A diverse scope of starting materials combined with an operationally simple, chromatography-free procedure make this a useful synthetic method for C2-functionalization of imidazole *N*-oxides.

4. Experimental

4.1. General

Unless otherwise noted, all the reagents were purchased from commercial suppliers, and used without further purification. Imidazole *N*-oxides **1a-d**[12–14] and oxime **13**[15] were prepared according to the reported procedures. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 300 MHz spectrometer or on a Bruker DRX500 500 MHz spectrometer in DMSO-d_6, chemical shift (δ) values for ^{1}H and ^{13}C NMR spectra are reported in parts per million (ppm) with the solvent resonance as the internal standard. High-resolution mass spectra (HRMS) were registered on Bruker MicrOTOF ESI-TOF mass spectrometer. The TLC analysis were performed with Merck Silica Gel 60 F_{254} precoated plates. IR spectra were recorded on a Shimadzu IRAffinity-1 FTIR spectrophotometer. The melting points were determined on a Kofler hot stage.

4.2. General procedure of preparation compounds 4a-w

Method A. A mixture of appropriate imidazole *N*-oxide (2 mmol), aldehyde (2 mmol) (or equivalent amount of 37% aqueous solution of formaldehyde in case of compounds **4a,e**) and barbituric acid **3a** (2 mmol) in mixture MeCN (5 mL) and water (2 mL) was refluxed for 8 h. The solvent was removed under reduced pressure and the residue was crystallized from IPA or its mixture with water to give the corresponding product.

Method B. A mixture of appropriate imidazole *N*-oxide (2 mmol), CH acid (2 mmol) and aldehyde (2 mmol) (or equivalent amount of 37% aqueous solution of formaldehyde in case of compound **4k,q,u**) in MeCN (5 mL) was refluxed for 6 h. The solvent was removed under reduced pressure and the residue was crystallized from IPA or its mixture with water to give the corresponding product.

4.2.1. *5-((1-Benzyl-3-hydroxy-4,5-dimethyl-1H-imidazol-3-ium-2-yl)methyl)-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-olate (**4a**)*

White powder; yield 88% (method A); mp > 300 °C; ^{1}H NMR (300 MHz, DMSO-d_6), δ: 10.16 (s, 2H), 7.38–7.27 (m, 3H), 7.11 (d, J = 6 Hz, 2H), 5.40 (s, 2H), 3.78 (s, 2H), 2.12 (s, 3H), 2.01 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 165.0, 150.6, 139.4, 135.2, 128.9, 127.9, 126.4, 122.5, 122.0, 81.4, 47.5, 16.2, 8.2, 6.7. IR spectrum, ν, cm^{-1}: 3434, 3114, 3035, 2973, 2832, 2757, 2498, 1685, 1612, 1481, 1455, 1383, 1356, 1303, 1293, 1225, 1186, 1106, 1045, 1031, 858, 821, 776, 698, 659, 576, 565, 539, 518, 444, 436. HRMS: Calculated for $C_{17}H_{19}N_4O_4$ $[M+H]^+$: 343.1406. Found: 343.1398.

4.2.2. *5-((1-Benzyl-3-hydroxy-4,5-dimethyl-1H-imidazol-3-ium-2-yl)(4-methoxyphenyl)methyl)-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-olate (**4b**)*

White powder; yield 96% (method A); mp 283–285 °C; ^{1}H NMR (300 MHz, DMSO-d_6), δ: 17.19 (s, 1H), 10.34 (s, 2H), 7.45–7.33 (m, 3H), 7.26 (d, J = 7.2 Hz, 2H), 6.77 (s, 4H), 6.07 (s, 1H), 5.52 (d, J = 16.8 Hz, 1H), 5.37 (d, J = 16.8 Hz, 1H), 3.70 (s, 3H), 2.24 (s, 3H), 2.13 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 165.2, 158.0, 150.6, 140.0, 135.3, 129.1, 128.1, 127.7, 127.6, 126.4, 123.0, 122.7, 113.6, 83.9, 55.0, 47.6, 32.4, 8.5, 6.8. IR spectrum, ν, cm^{-1}: 3440, 3137, 3033, 2997, 2963, 2832, 2760, 1690, 1601, 1510, 1473, 1457, 1391, 1352, 1300, 1273, 1248, 1220, 1169, 1093, 1042, 976, 884, 832, 801, 788, 772, 753, 705, 660, 574, 543, 536, 454, 436. HRMS: Calculated for $C_{24}H_{25}N_4O_5$ $[M+H]^+$: 449.1825. Found: 449.1819.

4.2.3. *5-((1-Benzyl-3-hydroxy-4,5-dimethyl-1H-imidazol-3-ium-2-yl)(thiophen-2-yl)methyl)-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-olate (**4c**)*

White powder; yield 73% (method A); mp 281–283 °C (dec.); ^{1}H NMR (300 MHz, DMSO-d_6), δ: 17.38 (s, 1H), 10.34 (s, 2H), 7.45–7.33 (m, 3H), 7.29 (d, J = 5.1 Hz, 1H), 7.21 (d, J = 7.5 Hz, 2H), 6.87 (t, J = 4.2 Hz, 1H), 6.57 (d, J = 2.7 Hz, 1H) 6.23 (s, 1H), 5.49 (d, J = 16.8 Hz, 1H), 5.40 (d, J = 16.8 Hz, 1H), 2.22 (s, 3H), 2.15 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 164.9, 150.5, 140.6, 138.5, 135.0,