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A Practical Synthesis of 2,4(5)-Diarylimidazoles from Simple Building Blocks

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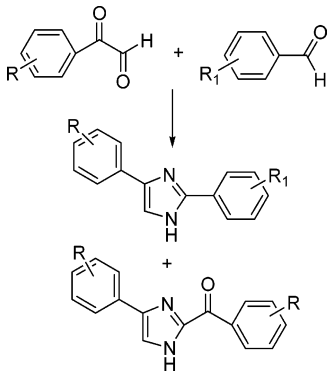

A simple and efficient approach to selectively obtain 2,4-(5)-diarylimidazoles suppressing formation of 2-aroyl-4(5)-arylimidazoles is described. The yield of each of the two products strongly depends on the reaction conditions employed. This reaction provides a simple method to prepare small libraries of biologically active compounds by parallel synthesis.

The imidazole ring system is one of the most important substructures found in a large number of natural products and pharmacologically active compounds. For example, the amino acid histidine, the hypnotic agent etomidate,[1] the antiulcerative agent cimetidine,[2] the proton pump inhibitor omeprazole,[3] the fungicide ketoconazole,[4] and the benzodiazepine antagonist flumazenil[5] are imidazole derivatives. Therefore, there is a continuous need for developing concise and practical synthetic methods for the preparation of imidazole and related compounds. Japp and Radziszewski proposed the first synthesis of the imidazole core in 1882, starting from 1,2-dicarbonyl compounds, aldehydes and ammonia, to obtain 2,4,5-triphenylimidazoles.[6,7] Subsequently, many other syntheses of this important heterocycle have been published.[8] For example, 2,4-diaryl-1*H*-imidazoles are often obtained from amidines and α-bromo arylketones.[9] Moreover, Zhang and Chen described an efficient procedure to obtain unsymmetrical, C5 unsubstituted 2,4-diarylimidazoles. In this approach acetophenones are oxidized *in situ* to α-tosyloxyacetophenones, which then condense with arylamidines to obtain the desired compounds.[10] Another important procedure to prepare imidazoles was described by Ueno and Togo. In this approach the heteroaromatic compounds were prepared reacting a polymer-supported [hydroxy(sulfonyloxy)iodo]benzene with ketones or alcohols, followed by the treatment with benzamidine.[11] Finally, it is also useful to mention the synthesis of 2,4-diarylimidazoles through Suzuki coupling, proposed by Langhammer and Erker.[12]

The aim of the present work was to prepare imidazoles introducing functionality in the C2 and C4 positions while leaving the C5 position unsubstituted, elaborating a simple and one-pot solution-phase synthesis methodology to produce a small library of biologically active compounds (e.g., 2,4(5)-diarylimidazoles are known to be NPY5 receptor antagonists).[13] The first step in designing a scaleable process was to identify a suitable synthetic route. Desirable characteristics would include a reduced number of synthetic and purification steps and commercially available starting materials. Subsequently, reaction conditions such as temperature, solvent, reaction times, and addition sequence of reactants were optimized, with the aim to obtain a versatile and high-yielding route. After evaluation of various synthetic procedures, we thought to modify Radziszewski's synthesis,[6] in particular using phenylglyoxals **1**, benzaldehydes **2**, and ammonium acetate as ammonia source (Scheme 1). Although this type of reaction is routinely used to build imidazoles, we found no examples concerning the preparation of C5 unsubstituted 2,4-diaryl-1*H*-imidazoles.

We found however that when using acetic acid as the solvent as reported in the literature, very low yields of the desired compounds **3** were obtained, and a high percentage of benzoylphenylimidazoles **4** was also formed. Thus, in our quest to improve the yields and the selectivity toward the initial 2,4(5)-diarylimidazole targets (**3**), we conducted the reaction modifying the temperature and the solvent, while keeping the reaction time unchanged (overnight). As shown in Table 1, these attempts at optimization were applied to the synthesis of the unsubstituted compound **3a**. However, after refluxing the reaction mixture in acetic acid, only decomposition products were detected.

Then, as reported in Table 1, we selected three solvents according to their characteristics to engage different types of

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SCHEME 1. Synthesis of Compounds of General Formula 3 and 4

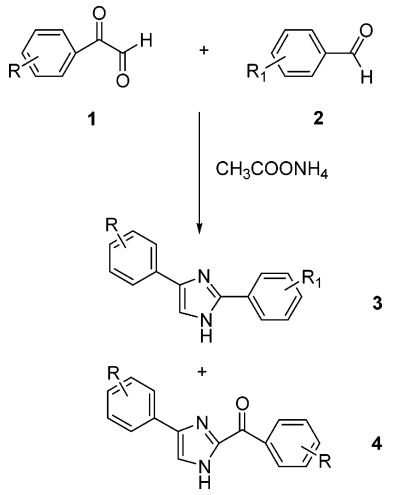
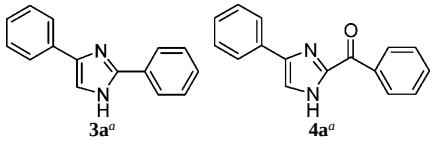


TABLE 1. Reaction Conditions Employed and Yields of the Products Synthesized



solvent	temperature	**3a**[a]	**4a**[a]
CH_3COOH	room temp	traces	77%
CH_3COOH	reflux	dec	dec
DCM	room temp	9%	91%
DMF	room temp	12%	78%
CH_3OH	room temp	83%	11%

[a] Chromatographic yields.

interactions with solutes: apolar aprotic, such as methylene chloride (DCM); polar aprotic, such as *N*,*N*-dimethylformamide (DMF); and polar protic, such as methanol. The results are reported in Table 1, together with the reaction condition employed.

As can be seen from Table 1, methanol at room temperature afforded the best yield in 2,4(5)-diphenylimidazole **3a** (83%), which we postulate arises from an equilibrium between the hydrated, hemiacetal, and aldehyde forms of phenylglyoxal (Figure 1).

In the presence of methanol, we postulate that these equilibria would be mainly shifted toward the hemiacetal form, and a formal benzaldehyde excess would effectively be present. This hypothesis is supported by NMR studies conducted on the dicarbonyl compound in chloroform-*d* ($CDCl_3$), in the absence or presence of 2 equiv of methanol (Figure 2). The ^1H NMR spectrum recorded in $CDCl_3$ without methanol (Figure 2a) shows a peak corresponding to the phenylglyoxal aldehyde group (9.70 ppm), thus confirming the presence of the dicarbonyl form.[14] This could be the reactive species in solvents such as DCM and DMF, supporting the autocondensation reaction and the formation of the benzoylphenylimidazole as the major component. The NMR spectrum recorded in $CDCl_3$ in presence of methanol (Figure 2b) shows instead a new peak near the methanolic methyl chemical shift (3.51 ppm), and the aldehyde peak disappears. This would confirm the existence of the

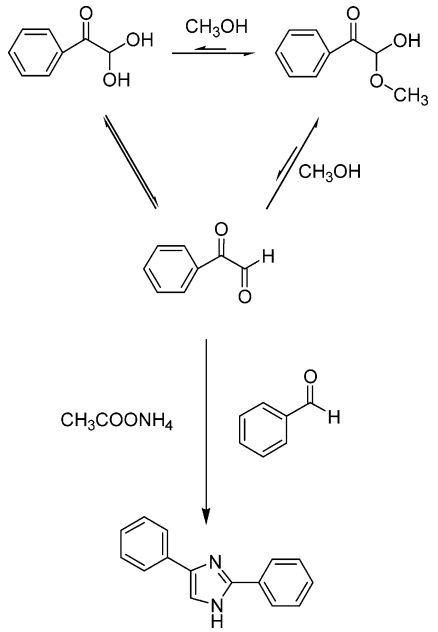


FIGURE 1. Probable equilibrium existing between the tautomers of the phenylglyoxal.

hemiacetal form, which supports formation of the desired 2,4-(5)-diphenylimidazole product.

This condition should favor the incorporation of benzaldehyde at the C2 position of the imidazole central core. The data reported in Table 1 suggest that, in other solvents, there is a competition between aldehyde and glyoxal for the C2 position of the heterocycle, with the preferred formation of the benzoylphenylimidazoles **4**.

This efficient synthetic route was then exploited in the preparation of a small library of compounds through parallel synthesis. The input selection was made with the aim to modify the electronic properties of the central core, considering the synthetic and, initially, the commercial accessibility of the starting building blocks. A series of substituted-2,4(5)-diphenylimidazoles were thus synthesized (Table 2).

The data reported in Table 2 show that all of the compounds synthesized were obtained in good yields with a simple workup and without chromatographic purification.

We also prepared two derivatives characterized by the presence of a pyridine ring in the 2 position of the imidazole central core (Figure 3).

The pyridine compounds were readily obtained in 77% yield (**3r**) and 71% yield (**3s**), thus indicating that the proposed synthetic route could be a viable and efficient way to prepare 2,4(5)-heteroarylimidazoles.

In summary, the described synthetic protocol allows for the preparation of a variety of 2,4(5)-diarylimidazoles through one-pot parallel synthesis, without the use of expensive or sensitive reagents. Moreover, a careful study of the reaction conditions allowed us to selectively prepare 2,4(5)-diarylimidazoles suppressing formation of unwanted 2-aroyl-4(5)-arylimidazoles. The products obtained belong to a class of biologically active compounds.

Experimental Section

Representative Procedure. Preparation of 3a. To a solution of benzaldehyde (0.70 mmol, 74 mg) and ammonium acetate

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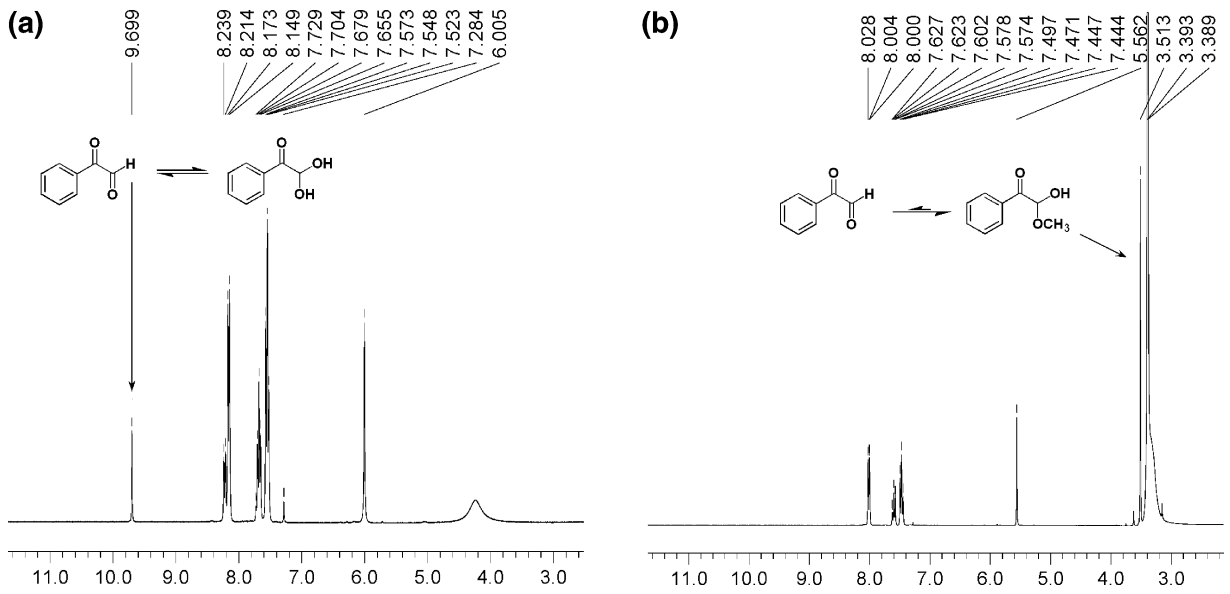
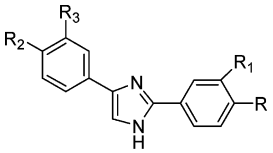


FIGURE 2. ^{1}H NMR spectra of the phenylglyoxal in $CDCl_3$ solutions recorded (a) without CH_3OH and (b) with 2 equiv of CH_3OH.

TABLE 2. 2,4(5)-Diarylimidazoles Synthesized

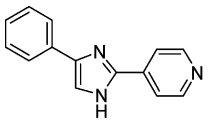


3a-q

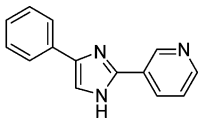
entry	R	R_1	R_2	R_3	yield (%)[a]
3a	H	H	H	H	83
3b	NO_2	H	H	H	68
3c	H	NO_2	H	H	59
3d	OCH_3	H	H	H	57
3e	H	OCH_3	H	H	62
3f	Cl	H	H	H	60
3g	H	Cl	H	H	56
3h	CF_3	H	H	H	74
3i	H	CF_3	H	H	66
3j	H	H	NO_2	H	65
3k	H	H	H	NO_2	52
3l	H	H	OCH_3	H	70
3m	H	H	H	OCH_3	57
3n	H	H	Cl	H	76
3o	H	H	H	Cl	83
3p	H	H	CF_3	H	65
3q	H	H	H	CF_3	81

[a] Isolated yields of analytically pure products.

(3.41 mmol, 262 mg) in methanol (3.5 mL) was added, over a period of 10 min, a solution of the commercially available phenylglyoxal monohydrate (0.70 mmol, 106 mg) in methanol (3.8 mL). The reaction mixture was stirred overnight at room temperature, then the solvent was evaporated, and the residue was partitioned between saturated aqueous $NaHCO_3$ solution (20 mL) and methylene chloride (20 mL). The organic phase was dried over Na_2SO_4, and the solvent was removed in vacuo. The selective isolation of either non-basic (2-benzoyl-4(5)-phenylimidazole) or basic (2,4(5)-diphenylimidazole) compounds from the crude reaction mixture was obtained using SCX-2 column (2 g, 30−90 μm, loading 0.4 mequiv/g). The column is prewashed with 1:1 DCM/methanol (10 mL), the non-basic products were eluted with methanol (10 mL), and then the desired 2,4(5)-diphenylimidazole was eluted with a 5% w/w methanolic ammonia solution (10 mL). The hydrochloride salt was prepared by treating the free base with a 5% w/w ethanolic HCl solution. The product was then crystallized from absolute ethanol/dry diethyl ether. **2,4(5)-Diphenylimidazole (3a).**[15] 83% yield, mp 274−275 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.46 (t, J = 7.23, 1H), 7.55 (t, J = 7.68, 2H), 7.66 (t, J = 3.24, 3H), 8.05 (d, J = 7.35, 2H), 8.30−8.33 (m, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 117.3, 123.9, 126.6, 127.7, 128.1, 129.7, 129.8, 129.9, 132.6, 134.5, 145.0. MS (EI) 221 [M^+]. Anal. Calcd for $C_{15}H_{12}N_2$·HCl: C, 70.17; H, 5.10; N, 10.91. Found: C, 69.85; H, 5.15; N, 10.59.



3r



3s

FIGURE 3. Pyridine compounds synthesized (3r, s).

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra and characterization data of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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