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Synthesis of 2-Keto-imidazoles Utilizing *N*-Arylamino-Substituted N-Heterocyclic Carbenes

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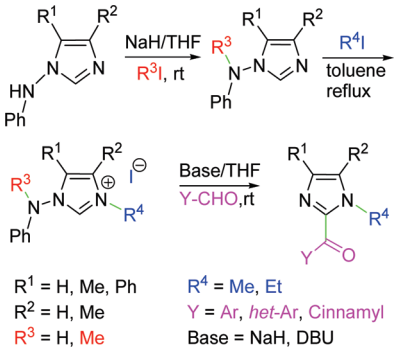

A new method for the synthesis of 2-aroyl-, 2-heteroaroyl-, and 2-cinnamoyl-substituted imidazoles in very good yields has been developed. The reaction employs novel nitrogen heterocyclic carbenes (NHCs), namely, *N*-arylamino-substituted NHCs, formed in situ from the corresponding imidazolium salts, and subsequent reaction with aromatic, heteroaromatic, and cinnamic aldehydes without utilizing transition metals or expensive specialized catalysts.

Present in numerous biologically active natural products and pharmaceuticals, nitrogen heterocycles are ideal targets for new synthetic methods. The embedded heteroatoms in such structures contribute electronic polarization and coordinating ability, which can be exploited to achieve regioselective reactivity. Synthetic methods that enable direct and selective heterocycle elaboration are invaluable tools for natural product synthesis and medicinal chemistry.

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. Recent advances in the imidazole-tailored ionic liquids,[6] stable nucleophilic carbenes,[7] and organic catalysts[8] are other applications of imidazole derivatives. Consequently, efforts are focused on the development of new methodologies for the synthesis and functionalization of imidazoles.

Relative to functionalizing imidazole at the 2-position, 2-lithioimidazoles are generated with *n*-BuLi at low temperatures under anhydrous conditions and then captured by electrophiles.[9] 2-Substituted imidazoles are also prepared by reacting 2-trimethylsilyl-1-alkylimidazoles with aldehydes[10] and by direct vinylation of 1-substituted imidazoles.[11] Very recently, C2-funcionalization by a vinyl ether group of 1-substituted imidazoles has been reported.[12] In addition, imidazoles can be thermally condensed with isocyanates,[13] whereas it was found that they can also be directly acylated in the 2-position by using either benzoylchloride and triethylamine[14] or 4-acetylmorpholine and *n*-BuLi.[15] However, when direct benzoylation was applied to the 4,5-dimethyl derivative, the corresponding 2-benzoylimidazole was formed in poor yield (19%).[16]

Concerning imidazole carbenes, their studies date back to the 1960s work of Wanzlick[17] and Öfele,[18] who although

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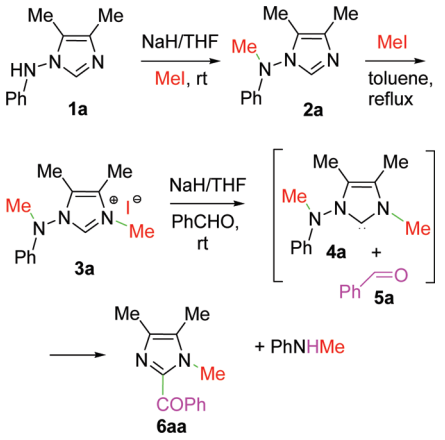
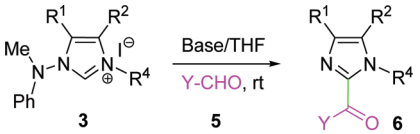
SCHEME 1. Synthesis of Benzoylimidazole 6aa via Carbene 4a



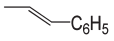
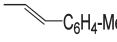
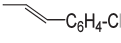
were unsuccessful in isolating any carbenes at that time, their work provided the conceptual framework for the development of chemistry of these species. The current growth in the chemistry of NHCs is mainly ascribed to the pioneering work of Arduengo and co-workers, who in 1991 isolated the first stable diamino carbene.[19] The role of NHCs as excellent ligands for transition metals[20] and their ability to catalyze various C−C coupling reactions, namely, benzoin condensation, transesterification,[21] and Stetter reaction,[22] have contributed significantly to the enormous interest in these compounds. Recently, there is also a growing awareness of their potential application as reagents in organic reactions[23] and especially in multicomponent reactions.[24]

Contrary to this literature background, with it being well-established that 2-acyl substitution in polysubstituted imidazoles is a rather difficult task, we sought to establish a new reaction for C2-functionalization of imidazoles involving formation of nitrogen heterocyclic carbenes (NHCs) and subsequent trapping with electrophiles to afford diverse 2-substituted imidazoles.

TABLE 1. Preparation of 2-Keto-Substituted Imidazoles



Base = NaH/ 1 h or DBU/ 4 h

Entry	3	R^1	R^2	R^4	5	Y	Prod	Yield (%)
1	**3a**	Me	Me	Me	**a**	C_6H_5	**6aa**	85
2	**3a**	Me	Me	Me	**b**	C_6H_4-Me-4	**6ab**	79
3	**3a**	Me	Me	Me	**c**	C_6H_4-Br-4	**6ac**	94
4	**3a**	Me	Me	Me	**d**	C_6H_4-Br-3	**6ad**	80
5	**3a**	Me	Me	Me	**e**	C_6H_4-Br-2	**6ae**	85
6	**3a**	Me	Me	Me	**f**	C_6H_4-Cl-4	**6af**	91
7	**3a**	Me	Me	Me	**g**	C_6H_4-CN-4	**6ag**	98
8	**3a**	Me	Me	Me	**h**	2-Furyl	**6ah**	79
9	**3a**	Me	Me	Me	**i**	2-Thienyl	**6ai**	70
10	**3a**	Me	Me	Me	**j**	3-Thienyl	**6aj**	72
11	**3b**	Ph	Me	Me	**b**	C_6H_4-Me-4	**6bb**	89
12	**3b**	Ph	Me	Me	**f**	C_6H_4-Cl-4	**6bf**	87
13	**3b**	Ph	Me	Me	**j**	3-Thienyl	**6bj**	91
14	**3c**	H	H	Me	**a**	C_6H_5	**6ca**	90
15	**3c**	H	H	Me	**f**	C_6H_4-Cl-4	**6cf**	92
16	**3d**	Me	Me	Et	**j**	3-Thienyl	**6dj**	90
17	**3a**	Me	Me	Me	**k**		**6ak**	82
18	**3a**	Me	Me	Me	**l**		**6al**	89
19	**3a**	Me	Me	Me	**m**		**6am**	87

The 4,5-dimethyl-3-phenylaminoimidazolium salt **3a**, formed in quantitative yield by methylation of **2a** with methyl iodide,[25] was chosen as a model compound because it would lead to the formation of a new Arduengo-type carbene with a liable 3-phenylamino substituent, arising thus the possibility of novel reactions and consequently offering to the whole scheme a new perspective.

Thus, **3a** was allowed to react with benzaldehyde in dry THF in the presence of either sodium hydride for 1 h or DBU for 4 h, whereupon the 2-benzoylimidazole **6aa** was isolated in 85% yield (Scheme 1). When the phenylamino salt **3e** was used, the reaction proceeded analogously, though much longer times (12 h) were necessary for the completion of the reaction.

The reaction also proceeded successfully with several 3-phenylaminoimidazolium salts and substituted aldehydes, including heterocyclic and α,β-unsaturated ones, with the corresponding 2-substituted imidazoles **6** always being isolated in very good yields (Table 1), proving thus the

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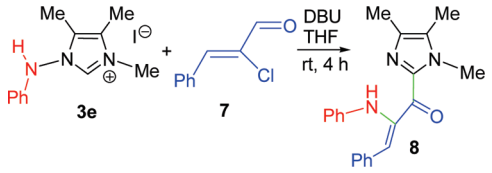
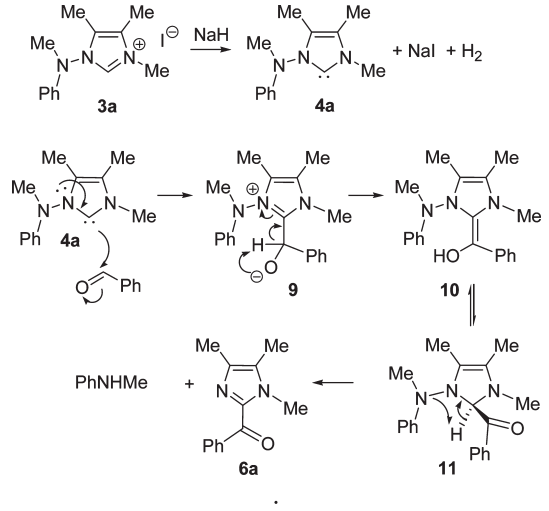
SCHEME 2. Reaction of Imidazolium Salt 3e with (*Z*)-α-Chlorocinnamaldehyde



SCHEME 3. Proposed Mechanism for the Reaction of Carbene 4a with Benzaldehyde



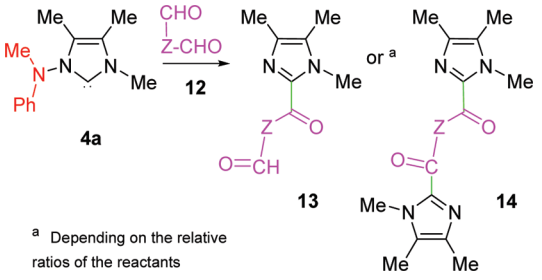
generality of the reaction. Moreover, in order to support the regioselectivity of the reaction leading exclusively to 2-substituted and not to the isomeric 4- or 5-keto-imidazoles, the nonsubstituted 1-phenylaminoimidazolium salt **3c** was prepared, which upon reaction with aldehydes **5a** and **5f** furnished the 2-keto-imidazoles **6ca** and **6cf** as the only reaction products.

The reaction of (*Z*)-α-chlorocinnamaldehyde (**7**) with carbenes **4** was also investigated, leading in the case of the reaction with the nonmethylated exonitrogen imidazolium salt **3e** to the unsaturated imidazolyl ketone **8** in 94% yield (Scheme 2). To the contrary, an unidentified mixture of resinous products was formed from the reaction with the methylated imidazolium salt **3a**.

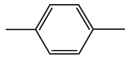
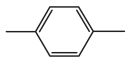
An unidentified mixture of resinous products was also formed when **3a** was allowed to react with sodium hydride in dry THF in the absence of aldehydes.

Concerning the reaction mechanism (Scheme 3), the initially formed Breslow intermediate tautomerizes to its more stable keto form (recently isolated and studied[26] in the case of the triazolydene carbene and benzaldehyde). However, due to the presence of the 3-arylamino substituent, the reaction does not follow the usual pathway to benzoin reaction.[27] Instead, aromatization through loss of the arylamino group, isolated and identified in the reaction products as *N*-methylaniline, results in the formation of the 2-aroyl-substituted

TABLE 2. Preparation of 2-Imidazole Derivatives 13 and 14



[a] Depending on the relative ratios of the reactants

Entry	**4a**:**12**	Aldehyde **12** Z	Prod	Yield (%)
1	1:1		**13a**	92
2	2:1		**14a**	91
3	1:1		**13b**	95
4	2:1		**14b**	97

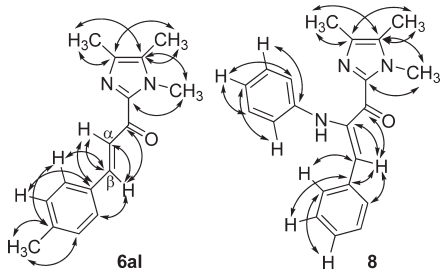


FIGURE 1. HMBC correlations between protons and carbons (via $^{2}J_{C-H}$ and $^{3}J_{C-H}$) in compounds **6al** and **8**.

imidazoles **6**. The formation of **8** possibly proceeds through an intramolecular nucleophilic vinylic substitution[28] reaction of the vinylic chlorine by the phenylamino group.

Finally, the reaction was studied with the bisaldehydes, isophthalaldehyde **12a** and terephthalaldehyde **12b**, whereupon depending on the molar ratio of the reactants either **13** or **14** was isolated in almost quantitative yield (Table 2).

All isolated 2-substituted imidazoles, with the exception of **6aa**, are novel compounds, and their structures were established by analysis of their IR, MS, NMR (^{1}H, ^{13}C, COSY, HMQC, HMBC), and elemental analysis data. In Figure 1, the HMBC correlations between protons and carbons (via $^{2}J_{C-H}$ and $^{3}J_{C-H}$) in compounds **6al** and **8** are depicted.

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The reaction described herein shows a new potential concerning carbene chemistry, leading to the synthesis of a variety of 2-substituted imidazoles. Furthermore, the incorporated 2-substituent can also be used as a convenient handle for further manipulation of the functionalized heterocycle. The facile and convenient reaction conditions, compared to existing procedures, make this reaction the method of choice in the preparation of 2-substituted imidazoles without utilizing transition metals or expensive specialized catalysts.

Experimental Section

General Procedure for the Preparation of 2-Keto-Imidazoles 6 and 13 and of Bisimidazoles 14 from Phenylaminoimidazoles 2. A solution of 1 mmol of **2** and of 1.5 mmol of methyl (or ethyl) iodide in 15 mL of dry toluene was refluxed for 30 min, and the precipitated solid was filtered off, affording almost quantitatively the ammonium salt **3**.

To a solution of 1 mmol of **3** and 1 mmol of aldehyde **5** (or **12**) in dry THF (20 mL) under argon atmosphere was added 1.1 mmol of sodium hydride (60% in oil), and the reaction mixture was stirred at rt for 1 h. After completion of the reaction (followed by TLC), it was quenched with water, and the organic layer was separated, washed with water, dried with sodium sulfate, filtered, and concentrated in vacuo. Flash chromatography on silica gel eluted with hexane−ethyl acetate (3:1) gave the substituted imidazoles **6** (or **13**). Using a half molar ratio of aldehyde **12**, only compounds **14** were obtained.

3,4,5-Trimethyl-1-[methyl(phenyl)amino]-1*H*-imidazol-3-ium iodide (3a): Light brown solid (97% yield); mp 143−145 °C; IR (KBr) ν_{max} 1638, 1595 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.09 (s, 3H, 5-CH_3), 2.35 (s, 3H, 4-CH_3), 3.56 (s, 3H, 1-NCH_3), 4.03 (s, 3H, 3-CH_3), 6.69 (d, J = 8.4 Hz, 2H, 2′, 6′-H), 7.04 (t, J = 7.4 Hz, 1H, 4′-H), 7.29−7.35 (m, 2H, 3′,5′-H), 9.88 (s, 1H, 2-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.1 (5-CH_3), 9.1 (4-CH_3), 35.2 (3-CH_3), 42.7 (1-NCH_3), 114.2 (C-2′,6′), 122.8 (C-4′), 127.1 (C-5), 127.4 (C-4), 129.7 (C-3′,5′), 135.9 (C-2), 146.6 (C-1′); MS (LCMS) m/z (%) 216 (100, M^+ − I). Anal. Calcd for $C_{13}H_{18}IN_3$ (343.21): C, 45.49; H, 5.29; N, 12.24%. Found: C, 45.38; H, 5.40; N, 12.12%.

2-Benzoyl-1,4,5-trimethyl-1*H*-imidazole (6aa): Yellowish oil, 85% yield; IR (neat) ν_{max} 1634 cm^{-1}; ^1H NMR δ 2.23 (s, 3H, 5-CH_3), 2.25 (s, 3H, 4-CH_3), 3.92 (s, 3H, 1-CH_3), 7.42−7.47 (m, 2H, 3′,5′-H), 7.52 (tt, J = 7.2, 1.5 Hz, 1H, 4′-H), 8.22 (d, J = 8.1 Hz, 2H, 2′,6′-H); ^{13}C NMR δ 9.1 (5-CH_3), 13.0 (4-CH_3), 33.1 (1-CH_3), 128.0 (C-3′,5′), 130.4 (C-5), 130.9 (C-2′,6′), 132.3 (C-4′), 136.0 (C-4), 138.1 (C-1′), 141.6 (C-2), 183.6 (CO); MS (LCMS) m/z (%) 215 (100, M^+ + H). Anal. Calcd for $C_{13}H_{14}N_2O$ (214.26): C, 72.87; H, 6.59; N, 13.07%. Found: C, 72.99; H, 6.45; N, 13.21%.

2-(3-Formylbenzoyl)-1,4,5-trimethyl-1*H*-imidazole (13a): White solid, 92% yield; mp 68−70 °C; IR (KBr) ν_{max} 1701, 1630 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.26 (s, 6H, 4-CH_3, 5-CH_3), 3.96 (s, 3H, 1-CH_3), 7.63 (t, J = 7.7 Hz, 1H, 5′-H), 8.06 (d, J = 7.7 Hz, 1H, 4′-H), 8.50 (d, J = 7.7 Hz, 1H, 6′-H), 8.74 (s, 1H, 2′-H), 10.1 (s, 1H, 4′-CHO); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.1 (5-CH_3), 13.0 (4-CH_3), 33.2 (1-CH_3), 128.8 (C-5′), 131.3 (C-5), 131.9 (C-2′), 133.2 (C-4′), 136.1 (C-4), 136.5 (C-6′), 136.7 (C-3′), 139.0 (C-1′), 141.0 (C-2), 182.0 (CO), 191.9 (4′-CO); MS (LCMS) m/z (%) 297 (100, M^+ + MeOH + Na), 275 (60, M^+ + MeOH + H), 265 (50, M^+ + Na), 243 (65, M^+ + H). Anal. Calcd for $C_{14}H_{14}N_2O_2$ (242.27): C, 69.41; H, 5.82; N, 11.56%. Found: C, 69.58; H, 5.69; N, 11.47%.

1,3-Bis[1,4,5-trimethyl-1*H*-imidazol-2-yl)carbonyl]benzene (14a): Yellowish solid, 91% yield; mp 147−149 °C; IR (KBr) ν_{max} 1619 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.23 (s, 6H, 5,5″-CH_3), 2.25 (s, 6H, 4,4″-CH_3), 3.94 (s, 6H, 1,1″-CH_3), 7.55 (t, J = 7.8 Hz, 1H, 5′-H), 8.44 (dd, J = 7.8, 1.6 Hz, 2H, 4′,6′-H), 9.06 (d, J = 1.6 Hz, 1H, 2′-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.1 (5,5″-CH_3), 13.1 (4,4″-CH_3), 33.1 (1,1″-CH_3), 127.7 (C-5′), 130.6 (C-5,5″), 133.3 (C-2′), 134.5 (C-4′,6′), 136.2 (C-4,4″), 137.9 (C-1′,3′), 141.4 (C-2,2″), 182.9 (2 × CO); MS (LCMS) m/z (%) 373 (50, M^+ + Na), 351 (100, M^+ + H). Anal. Calcd for $C_{20}H_{22}N_4O_2$ (350.41): C, 68.55; H, 6.33; N, 15.99%. Found: C, 68.39; H, 6.28; N, 16.05%.

By the same experimental procedure as above, reacting imidazolium salt **3e** and aldehyde **7** in 1:1 molar ratio imidazole derivative, **8** was obtained.

2-[(2*Z*)-2-Anilino-3-phenylprop-2-enoyl]-1,4,5-trimethyl-1*H*-imidazole (8): Yellow solid, 94% yield; mp 62−64 °C; IR (KBr) ν_{max} 1649 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.18 (s, 3H, 5-CH_3), 2.26 (s, 3H, 4-CH_3), 3.83 (s, 3H, 1-CH_3), 6.65 (dd, J = 8.7, 1.1 Hz, 2H, 2″,6″-H), 6.70 (tt, J = 7.4, 1.1 Hz, 1H, 4″-H), 7.05 (ddt, J = 8.5, 7.4, 1.9 Hz, 2H, 3″,5″-H), 7.12−7.25 (m, 3H, 3′,4′,5′-H), 7.51−7.54 (m, 2H, 2′,6′-H), 7.65 (s, 1H, β-H), 8.27 (br s, 1H, N-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.1 (5-CH_3), 12.9 (4-CH_3), 33.1 (1-CH_3), 116.4 (C-2″,6″), 119.4 (C-4″), 126.9 (C-β), 128.11 (C-3′,5′), 128.16 (C-4′), 128.7 (C-3″,5″), 130.2 (C-5), 130.6 (C-2′,6′), 135.1 (C-1′), 135.3 (C-4), 136.3 (C-α), 140.9 (C-2), 142.8 (C-1″), 181.1 (CO) (*double-primed values refer to N-Ph*); MS (LCMS) m/z (%) 332 (100, M^+ + H). Anal. Calcd for $C_{21}H_{21}N_3O$ (331.41): C, 76.11; H, 6.39, N, 12.68%. Found: C, 75.95; H, 6.45, N, 12.47%.

Supporting Information Available: Experimental details, compound characterization with full assignments of chemical shifts, and copies of ^1H NMR and ^{13}C NMR spectra for all novel compounds. This material is available free of charge via the Internet at http://pubs.acs.org.