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Synthesis of 1,2,4,5-Tetrasubstituted Imidazoles by a Sequential Aza-Wittig/Michael/Isomerization Reaction

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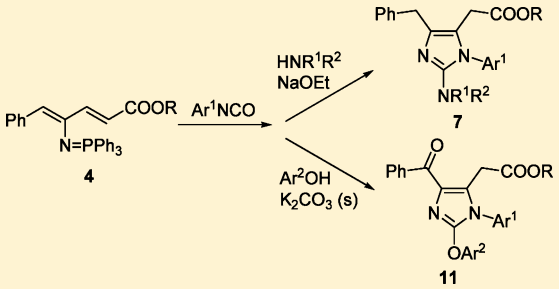
Supporting Information

ABSTRACT: Carbodiimides **4**, obtained from aza-Wittig reactions of iminophosphorane **3** with aryl isocyanates, reacted with secondary amines in the presence of a catalytic amount of sodium alkoxide to give 1,2,4,5-tetrasubstituted imidazoles **7** in good yields. However, 4-acylimidazoles **11** were obtained, as phenols were used in the presence of a catalytic amount of potassium carbonate due to further air oxidation of the expected products **10**.

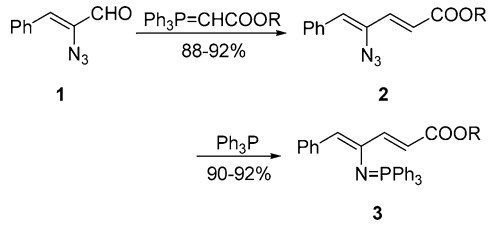


Multisubstituted imidazoles are a class of pharmaceutically important heterocyclic compounds and have been found to show widespread biological activities. A wide variety of derivatives of this ring system have been used as heme oxygenase-1 inhibitors,[1] HMG-CoA reductase inhibitors,[2] heme oxygenase inhibitors,[3] fatty acid amide hydrolase inhibitors,[4] γ-aminobutyric acid receptor agonists,[5] and $P2X_7$ receptor agonists.[6] Some of them have also been incorporated in marketed drugs such as cimetidine and losartan.[7] There are many known methods for the synthesis of imidazoles. For example, some imidazoles have been prepared by Ugi reaction and Davidson cyclization[8−10] or by reaction of imidazolium ylids and lithiated imidazoles,[11,12] and other imidazoles can be obtained starting from amino acids or *p*-toluenesulfonylmethyl isocyanide (TosMIC).[13−17] However, there is no general method for the synthesis of different functionalized imidazole derivatives, and 2-amino- or 2-aryloxy-substituted imidazoles were not easily accessible by currently existing routes. Consequently, new methodologies for the preparation of multisubstituted imidazoles are still desirable in synthetic organic and pharmaceutical chemistry.

The aza-Wittig reactions of iminophosphoranes have received increased attention in view of their utility in the synthesis of nitrogen heterocyclic compounds.[18] The carbodiimides, obtained efficiently by aza-Wittig reaction of iminophosphoranes with isocyanates under mild neutral conditions, can be used as synthetic intermediates of heterocycles by tandem processes involving aza-Wittig/intermolecular nucleophilic addition/intramolecular cyclizations. These tandem processes have been utilized previously in synthesis of imidazolones,[19] quinazolinones,[20] pteridin-4(3*H*)-ones,[21] pyrazinothienopyrimidinone,[22] and quinazolines.[23] We have also been interested in the synthesis of *N*-heterocycles through aza-Wittig reactions, with the aim of evaluating their biological activities.[24] Among them, indoles, fused pyrimidinones, and imidazolones were obtained efficiently via the tandem processes involving aza-Wittig/intermolecular nucleophilic addition/intramolecular cyclizations.[25] Here, we wish to report a new approach to the synthesis of 1,2,4,5-tetrasubstituted imidazoles by a new sequential aza-Wittig/Michael/isomerization reaction.

The α-azidocinnamaldehyde **1**, obtained from the reaction of α,β-dibromocinnamaldehyde with sodium azide,[26] reacted with alkoxycarbonylmethylidenetriphenylphosphorane to give the azide **2** in 88−92% yields. Further Staudinger reaction of azide **2** with triphenylphosphine at room temperature produced iminophosphorane **3** in high yields (Scheme 1).

Scheme 1



Reaction of iminophosphorane **3** with aromatic isocyanates at room temperature furnished the required carbodiimides **4** (Scheme 2), which were allowed to react with secondary amines to provide the guanidine intermediates **5**. Even in refluxing acetonitrile, **5** did not cyclize; however, in the presence of a catalytic amount of sodium ethoxide, **5** was converted directly to 1,2,4,5-tetrasubstituted imidazoles **7a−k** in satisfactory yields at room temperature. The results are listed in Table 1. The formation of **7** can be rationalized in terms of

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Scheme 2

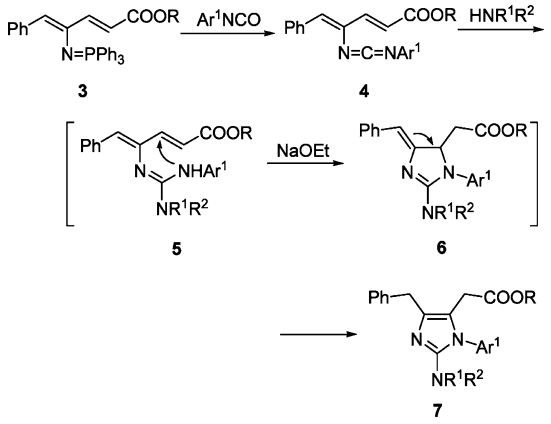


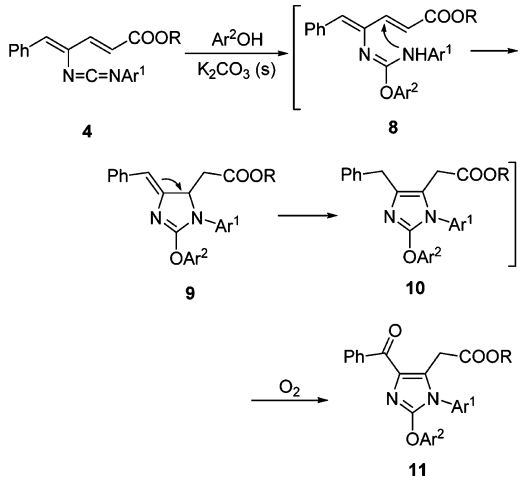
Table 1. Yields of Compounds 7a–k and 11a–g

entry	NR^1R^2/OAr^2	Ar^1	R	yield (%)
7a	morpholin-4-yl	4-Cl-C_6H_5	Et	86
7b	morpholin-4-yl	4-F-C_6H_5	Et	82
7c	morpholin-4-yl	3-Me-C_6H_5	Et	84
7d	morpholin-4-yl	4-Me-C_6H_5	Et	83
7e	morpholin-4-yl	4-Cl-C_6H_5	Me	87
7f	$N(Et)_2$	4-Cl-C_6H_5	Et	84
7g	$N(n\text{-}Bu)_2$	4-Cl-C_6H_5	Et	79
7h	piperidin-1-yl	4-Cl-C_6H_5	Et	80
7i	piperidin-1-yl	4-Cl-C_6H_5	Me	81
7j	pyrrolidin-1-yl	4-Cl-C_6H_5	Et	82
7k	pyrrolidin-1-yl	4-Cl-C_6H_5	Me	83
11a	4-Cl-C_6H_5O	C_6H_5	Et	67
11b	C_6H_5O	4-Cl-C_6H_5	Et	73
11c	4-Me-C_6H_5O	4-Cl-C_6H_5	Et	75
11d	2,4-2Cl-C_6H_5O	4-Cl-C_6H_5	Et	69
11e	4-Cl-C_6H_5O	4-Me-C_6H_5	Et	73
11f	4-Cl-C_6H_5O	4-Cl-C_6H_5	Et	72
11g	4-Cl-C_6H_5O	4-Me-C_6H_5	Me	62

an initial intramolecular Michael addition of the guanidine intermediates **5** under the catalysis of sodium ethoxide to give the dihydroimidazoles **6**, which isomerize through 1,3-H shift to give **7**.

The reactions of carbodiimides **4** with phenols were further examined in MeCN at 40–50 °C for 2–3 days, in the presence of a catalytic amount of potassium carbonate. To our surprise, the final products 4-phenacylimidazoles **11** were obtained directly from the reaction mixture instead of imidazoles **10** (Scheme 3). The results are listed in Table 1. As indicated in Table 1, the reaction is relatively insensitive to the presence or absence of substituents on the phenols, and the 2-aryloxy-4-phenacylimidazoles **11** can be obtained in 62–75% yields. The unexpected formation of **11** can be rationalized in terms of an initial nucleophilic addition of phenoxides to the carbodiimides **4** to give the intermediates **8**, which undertake intramolecular Michael addition to create the dihydroimidazoles **9** by the catalysis of potassium carbonate. Further isomerization of **9** through 1,3-H shift produces imidazoles **10**, which might be oxidized by air to give 4-phenacylimidazoles **11** under the reaction conditions. Although the reason for the above oxidixation is not yet very clear, it is deduced that 2-aryloxyimidazoles **10** are more easily oxidized than 2-amino-imidazoles **7**.

Scheme 3



The structures of imidazoles **7** and **11** were confirmed by their spectral data. Furthermore, a single crystal of **11b** was obtained from a CH_2Cl_2 solution of **11b**. X-ray structure analysis verified the proposed structure (Figure S1 in the Supporting Information).

In summary, we have developed an efficient synthesis of 1,2,4,5-substituted imidazoles via base-catalyzed reaction of functionalized carbodiimides with various amines or phenols. Because of the mild reaction conditions, good yields, and easily accessible starting material, we think that this new synthetic approach discussed here has potential in the synthesis of various 1,2,4,5-substituted imidazoles, which are of considerable interest as potential biologically active compounds or pharmaceuticals.

EXPERIMENTAL SECTION

Preparation of Azides 2. To a solution of alkoxycarbonylmethylidenetriphenylphosphorane (3 mmol) in dry methylene chloride (15 mL) was added 2-azido-cinnamaldehyde **1** (0.52 g, 3 mmol) at room temperature. After the reaction mixture was stirred for 2 h at ambient temperature, the solvent was removed under reduced pressure, and the residue was purified by chromatography eluting with Et_2O/petroleum ether 1:2 to give azides **2**.

*Ethyl 4-Azido-5-phenylpenta-2,4-dienoate (**2a**).* Light yellow oil (yield 88%): IR (KBr, cm^{-1}) 2112, 1716, 1624, 1447, 1368, 1306, 1264, 1156, 1036, 972, 693; ^1H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.64–7.26 (m, 6H), 6.38 (s, 1H), 6.27 (d, J = 15.6 Hz, 1H), 4.26 (q, J = 7.2 Hz, 2H), 1.34 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 166.2, 140.6, 133.6, 132.4, 129.6, 128.8, 128.5, 127.5, 119.3, 60.7, 14.2.

*Methyl 4-Azido-5-phenylpenta-2,4-dienoate (**2b**).* Light yellow oil (yield 92%): IR (KBr, cm^{-1}) 2105, 1716, 1625, 1434, 1384, 1309, 1266, 1197, 1163, 982, 916, 852, 748, 690; ^1H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.64–7.26 (m, 6H), 6.38 (s, 1H), 6.28 (d, J = 15.6 Hz, 1H), 3.81 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 166.7, 140.9, 133.5, 132.3, 129.6, 128.8, 128.5, 127.7, 118.7, 51.8.

Preparation of Iminophosphosphorane 3. To a stirred solution of **2a** (5 mmol) in methylene dichloride (10 mL) was added dropwise triphenylphosphine (1.31 g, 5 mmol) in methylene dichloride (10 mL) at room temperature. After the reaction mixture was stirred for 2 h at ambient temperature, the solvent was removed under reduced pressure, and the residual was purified by chromatography eluting with Et_2O/petroleum ether 1:2 to give iminophosphosphorane **3** as yellow solid.

*Ethyl 5-Phenyl-4-((triphenylphosphoranylidene)amino)penta-2,4-dienoate (**3a**).* Yellow solid (yield 90%): mp 96–98 °C; ^1H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.82–7.02 (m, 21H), 6.08 (s, 1H),

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5.73 (d, J = 15.6 Hz, 1H), 4.02 (q, J = 7.2 Hz, 2H), 1.16 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 167.2, 149.2, 132.5, 132.0, 131.7, 131.4, 128.9, 128.7, 128.4, 127.8, 127.6, 125.3, 117.5, 59.6, 14.2; MS (EI, 70 eV) m/z (%) 477 (M^+, 2), 407 (34), 378 (14), 277 (44), 262 (87), 239 (75), 183 (100), 133 (48). Anal. Calcd for $C_{31}H_{28}NO_2P$: C, 77.97; H, 5.91; N, 2.93. Found: C, 77.83; H, 6.04; N, 3.08.

*Methyl 5-Phenyl-4-((triphenylphosphoranylidene)amino)penta-2,4-dienoate (**3b**).* Yellow solid (yield 92%): mp 124−125 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.82−7.02 (m, 21H), 6.08 (s, 1H), 5.76 (d, J = 15.6 Hz, 1H), 3.57 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 167.8, 149.8, 143.7, 138.4, 132.6, 132.2, 131.5, 128.8, 128.5, 127.7, 127.4, 120.4, 117.0, 51.1; MS (EI, 70 eV) m/z (%) 463 (M^+, 2), 404 (38), 378 (13), 277 (26), 262 (56), 185 (100), 108 (35). Anal. Calcd for $C_{30}H_{26}NO_2P$: C, 77.74; H, 5.65; N, 3.02. Found: C, 77.97; H, 5.84; N, 2.98.

General Procedure for Preparation of 1,2,4,5-Tetrasubstituted Imidazoles 7a−k. To a solution of iminophosphorane **3** (3 mmol) in dry methylene dichloride (15 mL) was added aromatic isocyanate (3 mmol) at room temperature. After the reaction mixture was left to stand for 20 min at room temperature, the secondary amine R^1R^2NH (3 mmol) was added. The reaction mixture was allowed to be stirred for 0.5−1 h, and then the solvent was removed, and anhydrous ethanol (10 mL) with EtONa (0.3 mmol, 10% equiv) in EtOH was added. The mixture was stirred for 2−4 h at room temperature. The solution was concentrated under reduced pressure, and the residue was subjected to chromatography on silica gel eluting with Et_2O/petroleum ether 1:3 to give **7a−k**.

*Ethyl 2-(4-Benzyl-1-(4-chlorophenyl)-2-morpholino-1H-imidazol-5-yl)acetate (**7a**).* White solid (yield 86%): mp 93−94 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.44−7.43 (m, 2H), 7.30−7.25 (m,, 6H), 7.18−7.16 (m, 1H), 3.93−3.90 (m, 4H), 3.57−3.55 (m, 4H), 3.26 (s, 2H), 2.98−2.96 (m, 4H), 1.10 (t, J = 14.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 169.7, 151.0, 139.9, 135.2, 134.9, 134.1, 129.6, 128.9, 128.7, 128.6, 128.4, 128.2, 128.0, 125.8, 125.6, 118.7, 66.3, 60.8, 49.7, 33.5, 29.5, 14.0, 13.6; MS (EI, 70 eV) m/z (%) 439 (M^+, 40), 382 (10), 366 (100), 218 (7), 138 (11), 128 (11), 117 (16). Anal. Calcd for $C_{24}H_{26}ClN_3O_3$: C, 65.52; H, 5.96; N, 9.55. Found: C, 65.79; H, 6.03; N, 9.78.

*Ethyl 2-(4-Benzyl-1-(4-fluorophenyl)-2-morpholino-1H-imidazol-5-yl)acetate (**7b**).* White solid (yield 82%): mp 104−106 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.33−7.15 (m, 9H), 3.93−3.90 (m, 4H), 3.57−3.53 (m, 4H), 3.26 (s, 2H), 2.99−2.95 (m, 4H), 1.10 (t, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 169.8, 161.9, 151.1, 139.9, 135.0, 132.4, 129.4, 129.3, 128.6, 128.4, 128.2, 128.0, 125.8, 125.6, 118.9, 116.4, 116.3, 116.1, 66.4, 60.8, 49.8, 33.6, 29.6, 14.1; MS (EI, 70 eV) m/z (%) 423 (M^+, 32), 366 (100), 218 (15), 138 (27), 128 (46), 117 (58). Anal. Calcd for $C_{24}H_{26}FN_3O_3$: C, 68.07; H, 6.19; N, 9.92. Found: C, 68.16; H, 6.08; N, 9.68.

*Ethyl 2-(4-Benzyl-2-morpholino-1-(m-tolyl)-1H-imidazol-5-yl)-acetate (**7c**).* White solid (yield 84%): mp 61−63 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.34−7.12 (m, 9H), 3.92−3.89 (m, 4H), 3.55−3.52 (m, 4H), 3.27 (s, 2H), 2.99−2.96 (m, 4H), 2.38 (s, 3H), 1.09 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 169.9, 150.9, 140.1, 139.3, 136.3, 134.6, 129.1, 128.9, 128.6, 128.4, 128.1, 128.0, 127.8, 125.8, 125.6, 124.5, 118.8, 66.4, 60.6, 49.6, 33.5, 29.7, 21.1, 14.1, 13.7; MS (EI, 70 eV) m/z (%) 419 (M^+, 39), 362 (9), 346 (100), 277 (21), 199 (5), 128 (5), 118 (9), 106 (6), 91 (24). Anal. Calcd for $C_{25}H_{29}N_3O_3$: C, 71.57; H, 6.97; N, 10.02. Found: C, 71.69; H, 7.20; N, 10.25.

*Ethyl 2-(4-Benzyl-2-morpholino-1-(p-tolyl)-1H-imidazol-5-yl)-acetate (**7d**).* White solid (yield 83%): mp 64−65 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.29−7.17 (m, 9H), 3.92−3.90 (m, 4H), 3.56−3.53 (m, 4H), 3.25 (s, 2H), 2.99−1.97 (m, 4H), 2.40 (s, 3H), 1.09 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 170.0, 151.0, 140.1, 138.2, 134.5, 133.7, 130.0, 129.8, 128.6, 128.5, 128.2, 128.0, 127.4, 127.2, 125.8, 119.0, 66.4, 60.7, 49.6, 33.5, 29.7, 21.1, 14.1, 13.7; MS (EI, 70 eV) m/z (%) 419 (M^+, 38), 362 (8), 346 (100), 144 (3), 118 (7), 91 (16). Anal. Calcd for $C_{25}H_{29}N_3O_3$: C, 71.57; H, 6.97; N, 10.02. Found: C, 71.82; H, 7.23; N, 10.28.

*Methyl 2-(4-Benzyl-1-(4-chlorophenyl)-2-morpholino-1H-imidazol-5-yl)acetate (**7e**).* White solid (yield 87%): mp 94−96 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.69−7.18 (m, 9H), 3.91 (s, 2H), 3.58−3.54 (m, 4H), 3.47 (s, 3H), 3.27 (s, 2H), 2.99−2.95 (m, 4H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 170.2, 151.0, 139.8, 135.2, 134.8, 134.1, 132.0, 131.9, 131.8, 129.6, 128.8, 128.5, 128.4, 128.3, 128.1, 125.8, 118.5, 66.3, 51.8, 49.7, 33.6, 29.3; MS (EI, 70 eV) m/z (%) 425 (M^+, 50), 366 (100), 277 (14), 138 (12), 128 (11), 117 (18), 91 (14). Anal. Calcd for $C_{23}H_{24}ClN_3O_3$: C, 64.86; H, 5.68; N, 9.87. Found: C, 64.98; H, 5.81; N, 10.06.

*Ethyl 2-(4-Benzyl-1-(4-chlorophenyl)-2-(diethylamino)-1H-imidazol-5-yl)acetate (**7f**).* White solid (yield 84%): mp 56−57 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.42−7.16 (m, 9H), 3.93−3.89 (m, 4H), 3.24 (s, 2H), 2.94 (q, J = 7.2 Hz, 4H), 1.09 (t, J = 7.2 Hz, 3H), 0.92 (t, J = 7.2 Hz, 6H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 169.9, 151.0, 140.2, 135.2, 135.1, 133.9, 129.5, 129.3, 129.2, 128.5, 128.3, 128.2, 127.9, 125.8, 125.6, 118.3, 60.7, 46.1, 33.5, 29.7, 13.6, 13.2, 12.3; MS (EI, 70 eV) m/z (%) 425 (M^+, 37), 352 (100), 286 (17), 138 (10), 128 (7), 117 (14), 91 (14). Anal. Calcd for $C_{24}H_{28}ClN_3O_2$: C, 67.67; H, 6.63; N, 9.87. Found: C, 67.83; H, 6.49; N, 10.11.

*Ethyl 2-(4-Benzyl-1-(4-chlorophenyl)-2-(dibutylamino)-1H-imidazol-5-yl)acetate (**7g**).* White solid (yield 79%): mp 45−47 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.42−7.15 (m, 9H), 3.92−3.88 (m, 4H), 3.23 (s, 2H), 2.87 (t, J = 7.2 Hz, 4H), 1.32−1.12 (m, 8H), 1.08 (t, J = 7.2 Hz, 3H), 0.81 (t, J = 7.2 Hz, 6H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 170.0, 151.7, 140.3, 135.4, 135.1, 134.0, 129.6, 129.4, 128.6, 128.4, 128.2, 128.0, 125.8, 118.1, 60.8, 51.8, 33.5, 29.7, 20.1, 14.1, 13.7; MS (EI, 70 eV) m/z (%) 481 (M^+, 44), 408 (77), 382 (100), 272 (20), 138 (23), 125 (16), 117 (24), 91 (29). Anal. Calcd for $C_{28}H_{36}ClN_3O_2$: C, 69.76; H, 7.53; N, 8.72. Found: C, 69.89; H, 7.72; N, 8.96.

*Ethyl 2-(4-Benzyl-1-(4-chlorophenyl)-2-(piperidin-1-yl)-1H-imidazol-5-yl)acetate (**7h**).* White solid, (yield 80%): mp 50−51 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.42−7.16 (m, 9H), 3.92−3.89 (m, 4H), 3.26 (s, 2H), 2.92 (t, J = 4.8 Hz, 4H), 1.43−1.40 (m, 6H), 1.09 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 170.0, 152.4, 140.1, 135.4, 135.0, 133.7, 129.4, 128.8, 128.6, 128.1, 125.8, 118.1, 60.8, 50.8, 33.6, 29.8, 25.5, 24.0, 13.9; MS (EI, 70 eV) m/z (%) 437 (M^+, 40), 408 (4), 366 (37), 364 (100), 218 (6), 138 (10), 128 (9), 117 (13), 91 (10). Anal. Calcd for $C_{25}H_{28}ClN_3O_2$: C, 68.56; H, 6.44; N, 9.59. Found: C, 68.62; H, 6.56; N, 9.78.

*Methyl 2-(4-Benzyl-1-(4-chlorophenyl)-2-(piperidin-1-yl)-1H-imidazol-5-yl)acetate (**7i**).* White solid (yield 81%): mp 62−63 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.43−7.16 (m, 9H), 3.91 (s, 2H), 3.45 (s, 3H), 3.26 (s, 2H), 2.92 (t, J = 4.8 Hz, 4H), 1.48−1.32 (m, 6H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 170.3, 152.4, 140.0, 135.3, 135.0, 133.7, 129.4, 128.7, 128.6, 128.1, 125.7, 117.9, 51.8, 50.7, 33.6, 29.4, 25.4; MS (EI, 70 eV) m/z (%) 423 (M^+, 47), 366 (30), 364 (100), 218 (4), 138 (10), 128 (6), 117 (15), 111 (13), 91 (11). Anal. Calcd for $C_{24}H_{26}ClN_3O_2$: C, 68.00; H, 6.18; N, 9.91. Found: C, 68.27; H, 6.46; N, 10.12.

*Ethyl 2-(4-Benzyl-1-(4-chlorophenyl)-2-(pyrrolidin-1-yl)-1H-imidazol-5-yl)acetate (**7j**).* White solid (yield 82%): mp 53−55 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.40−7.15 (m, 9H), 3.92−3.90 (m, 4H), 3.18 (s, 2H), 3.06 (t, J = 6.6 Hz, 4H), 1.76−1.73 (m, 4H), 1.10 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 170.2, 151.3, 140.2, 135.8, 134.6, 134.1, 129.9, 129.3, 128.6, 128.1, 125.8, 117.9, 60.8, 49.7, 33.7, 29.6, 25.2, 13.9; MS (EI, 70 eV) m/z (%) 423 (M^+, 27), 352 (32), 350 (100), 218 (6), 138 (8), 128 (6), 117 (11), 91 (8). Anal. Calcd for $C_{24}H_{26}ClN_3O_2$: C, 68.00; H, 6.18; N, 9.91. Found: C, 68.18; H, 6.01; N, 10.15.

*Methyl 2-(4-Benzyl-1-(4-chlorophenyl)-2-(pyrrolidin-1-yl)-1H-imidazol-5-yl)acetate (**7k**).* White solid (yield 83%): mp 68−69 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.41−7.15 (m, 9H), 3.89 (s, 2H), 3.46 (s, 3H), 3.18 (s, 2H), 3.06 (t, J = 6.6 Hz, 4H), 1.76−1.73 (m, 4H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 170.6, 151.3, 140.1, 135.7, 134.6, 134.1, 129.9, 129.3, 128.6, 128.1, 125.7, 117.3, 51.7, 49.6, 33.7, 29.3, 25.1; MS (EI, 70 eV) m/z (%) 409 (M^+, 34), 352 (35), 350 (100), 334 (16), 218 (7), 138 (10), 128 (6), 117 (11), 91 (10). Anal.

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Calcd for $C_{23}H_{24}ClN_3O_2$: C, 67.39; H, 5.90; N, 10.25. Found: C, 67.62; H, 5.72; N, 10.19.

Isolation of the Guanidine Intermediate 5c. To a solution of iminophosphorane **3a** (1.43 g, 3 mmol) in dry methylene dichloride (15 mL) was added 3-methylphenylisocyanate (0.40 g, 3 mmol) at room temperature. After the reaction mixture was left to stand for 20 min at room temperature, to the reaction mixture was added morpholine (0.26 g, 3 mmol). The reaction mixture was stirred at ambient temperature for 2 h until a solid precipitated. The solid formed was filtered off and recrystallized from ethanol/petroleum ether (1:1) to give **5c** as white solid.

*Ethyl 4-((Morpholino(m-tolylamino)methylene)amino)-5-phenylpenta-2,4-dienoate (**5c**).* White solid: mp 163−164 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.63−6.63 (m, 10H), 6.21 (s, 1H), 5.96 (d, J = 15.0 Hz, 1H), 5.56 (s, 1H), 4.17 (q, J = 7.2 Hz, 2H), 3.75−3.67 (m, 4H), 3.45−3.35 (m, 4H), 2.22 (s, 3H), 1.28 (t, J = 7.2 Hz, 3H); ^{13}C NMR (DMSO, 150 MHz) δ (ppm) 166.4, 150.2, 150.1, 146.0, 143.6, 140.9, 140.8, 137.4, 137.3, 128.9, 128.1, 126.6, 122.7, 121.9, 119.4, 115.7, 66.0, 59.6, 47.1, 20.7, 14.2; MS (EI, 70 eV) m/z (%) 419 (M^+, 40), 390 (4), 346 (100), 203 (9), 91 (25). Anal. Calcd for $C_{25}H_{29}N_3O_3$: C, 71.57; H, 6.97; N, 10.02. Found: C, 71.78; H, 6.81; N, 10.27.

General Procedure for Preparation of 4-Phenacylimidazoles 11a−11g. To the above prepared carbodiimide **4** in CH_3CN (10 mL) were added phenol (3 mmol) and potassium carbonate (0.04 g, 0.3 mmol). The reaction mixture was stirred for 2−3 days at 40−50 °C. The solution was then concentrated under reduced pressure, and the residue was subjected to chromatography on silica gel eluting with Et_2O/petroleum ether 1:4 to give **11a−g**.

*Ethyl 2-(4-Benzoyl-2-(4-chlorophenoxy)-1-phenyl-1H-imidazol-5-yl)acetate (**11a**).* Light yellow solid (yield 67%): mp 127−129 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.30 (d, J = 7.6 Hz, 2H), 7.52−7.19 (m, 12H), 4.13 (q, J = 7.2 Hz, 2H), 3.93 (s, 2H), 1.21 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 188.3, 169.3, 153.1, 147.6, 137.8, 133.1, 132.9, 132.1, 131.6, 130.4, 129.6, 129.4, 129.2, 127.9, 127.5, 119.7, 116.6, 61.3, 31.3, 14.1; MS (EI, 70 eV) m/z (%) 460 (M^+, 30), 414 (87), 387 (40), 276 (17), 247 (18), 204 (14), 139 (14), 111 (28), 105 (59), 91 (11), 11 (100). Anal. Calcd for $C_{26}H_{21}ClN_2O_4$: C, 67.75; H, 4.59; N, 6.08. Found: C, 68.01; H, 4.82; N, 6.02.

*Ethyl 2-(4-Benzoyl-1-(4-chlorophenyl)-2-phenoxy-1H-imidazol-5-yl)acetate (**11b**).* Light yellow solid (yield 73%): mp 141−143 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 8.31−8.30 (m, 2H), 7.51−7.48 (m, 3H), 7.44−7.42 (m, 2H), 7.34−7.32 (m, 4H), 7.24−7.22 (m, 2H), 7.14 (m, 1H), 4.16−4.13 (m, 2H), 3.93 (s, 2H), 1.23 (t, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 188.2, 169.3, 154.6, 147.7, 137.7, 135.7, 133.3, 132.1, 131.4, 131.2, 130.5, 129.8, 129.5, 128.8, 127.8, 124.5, 118.1, 61.3, 31.2, 14.1; MS (EI, 70 eV) m/z (%) 460 (M^+, 27), 414 (57), 387 (35), 310 (7), 247 (6), 204 (8), 152 (5), 111 (8), 105 (66), 77 (100). Anal. Calcd for $C_{26}H_{21}ClN_2O_4$: C, 67.75; H, 4.59; N, 6.08. Found: C, 67.98; H, 4.73; N, 6.33.

*Ethyl 2-(4-Benzoyl-1-(4-chlorophenyl)-2-(p-tolyloxy)-1H-imidazol-5-yl)acetate (**11c**).* Light yellow solid (yield 75%): mp 156−158 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 8.31 (d, J = 7.8 Hz, 2H), 7.52−7.12 (m, 11H), 4.14 (q, J = 7.2 Hz, 2H), 3.93 (s, 2H), 2.31 (s, 3H), 1.23 (t, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 188.2, 169.3, 152.4, 148.0, 137.7, 135.6, 134.1, 133.3, 132.1, 131.5, 131.0, 130.5, 129.9, 129.8, 128.8, 127.8, 118.0, 61.3, 31.2, 20.6, 14.0; MS (EI, 70 eV) m/z (%) 474 (M^+, 40), 428 (97), 400 (23), 294 (10), 204 (11), 119 (13), 111 (10), 105 (100), 91 (56), 77 (83). Anal. Calcd for $C_{27}H_{23}ClN_2O_4$: C, 68.28; H, 4.88; N, 5.90. Found: C, 68.02; H, 5.07; N, 6.15.

*Ethyl 2-(4-Benzoyl-1-(4-chlorophenyl)-2-(2,4-dichlorophenoxy)-1H-imidazol-5-yl)acetate (**11d**).* White solid (yield 69%): mp 173−175 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 8.23 (d, J = 7.8 Hz, 2H), 7.53−7.24 (m, 10H), 4.16 (q, J = 7.2 Hz, 2H), 3.92 (s, 2H), 1.24 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 188.0, 169.2, 148.2, 147.4, 137.5, 135.8, 133.1, 132.2, 131.3, 131.1, 130.7, 130.4, 130.1, 129.9, 128.8, 127.9, 127.8, 125.9, 122.1, 61.4, 31.1, 14.1; MS (EI, 70 eV) m/z (%) 528 (M^+, 19), 484 (74), 310 (15), 247 (18), 204 (10), 145 (14), 129 (11), 111 (21), 105 (100), 77 (99). Anal. Calcd for $C_{26}H_{19}Cl_3N_2O_4$: C, 58.94; H, 3.61; N, 5.29. Found: C, 59.21; H, 3.44; N, 5.10.

*Ethyl 2-(4-Benzoyl-2-(4-chlorophenoxy)-1-(p-tolyl)-1H-imidazol-5-yl)acetate (**11e**).* Light yellow solid (yield 73%): mp 150−152 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 8.29 (d, J = 7.2 Hz, 2H), 7.52−7.19 (m, 11H), 4.14 (q, J = 6.0 Hz, 2H), 3.92 (s, 2H), 2.43 (s, 3H), 1.22 (t, J = 6.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 188.1, 169.3, 153.1, 147.6, 139.9, 137.8, 132.9, 132.0, 131.7, 130.4, 130.2, 130.1, 129.4, 129.3, 127.8, 127.1, 119.6, 61.2, 31.2, 21.2, 14.0; MS (EI, 70 eV) m/z (%) 474 (M^+, 37), 428 (100), 401 (45), 317 (14), 290 (16), 274 (13), 261 (11), 247 (15), 139 (14), 111 (22), 105 (78), 91 (34), 77 (74). Anal. Calcd for $C_{27}H_{23}ClN_2O_4$: C, 68.28; H, 4.88; N, 5.90. Found: C, 68.39; H, 5.02; N, 5.72.

*Ethyl 2-(4-Benzoyl-2-(4-chlorophenoxy)-1-(4-chlorophenyl)-1H-imidazol-5-yl)acetate (**11f**).* Light yellow solid (yield 72%): mp 170−172 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 8.28 (d, J = 7.2 Hz, 2H), 7.53−7.21 (m, 11H), 4.15 (q, J = 7.2 Hz, 2H), 3.92 (s, 2H), 1.24 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 188.2, 169.3, 152.9, 147.5, 137.7, 135.9, 133.3, 132.3, 131.3, 130.5, 130.0, 129.8, 129.5, 128.9, 127.9, 119.7, 61.4, 31.2, 14.1; MS (EI, 70 eV) m/z (%) 494 (M^+, 24), 448 (69), 420 (33), 310 (14), 247 (14), 204 (14), 139 (16), 111 (47), 105 (93), 77 (100). Anal. Calcd for $C_{26}H_{20}Cl_2N_2O_4$: C, 63.04; H, 4.07; N, 5.66. Found: C, 63.26; H, 4.33; N, 5.89.

*Methyl 2-(4-Benzoyl-2-(4-chlorophenoxy)-1-(p-tolyl)-1H-imidazol-5-yl)acetate (**11g**).* Light yellow solid (yield 62%): mp 172−173 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 8.30 (d, J = 7.8 Hz, 2H), 7.52−7.20 (m, 11H), 3.92 (s, 2H), 3.69 (s, 3H), 2.43 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 188.2, 169.8, 153.1, 147.7, 140.0, 137.8, 133.0, 132.1, 131.6, 130.5, 130.4, 130.3, 130.1, 129.5, 129.4, 127.9, 127.2, 119.7, 52.3, 31.0, 21.2; MS (EI, 70 eV) m/z (%) 460 (M^+, 30), 428 (95), 401 (33), 317 (12), 247 (17), 204 (12), 157 (12), 139 (18), 111 (31), 105 (100). Anal. Calcd for $C_{26}H_{21}ClN_2O_4$: C, 67.75; H, 4.59; N, 6.08. Found: C, 67.94; H, 4.86; N, 6.25.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H NMR and ^{13}C NMR spectra for compounds **2**, **3**, **7**, and **11** and crystal data for **11b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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