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AN EFFICIENT AND CONVENIENT METHOD FOR SYNTHESIS OF 1-SUBSTITUTED IMIDAZOLES

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Abstract – A convenient method for the synthesis 1-substituted imidazoles was developed by the reaction of α-bromoketone with lithium imidazolide. The reaction gave the desired products in improved yields without the formation of 1,3-disubstituted imidazolium salts. Treatment of bromoacetaldehyde ethylene acetal, 2-(bromomethyl)tetrahydro-2*H*-pyran, and *N*-(bromomethyl)phthalimide with lithium imidazolide also gave the corresponding 1-substituted imidazole in good to excellent yields. Direct reaction of α-bromoketone with imidazole as control experiment afforded undesired 1,3-disubstituted imidazolium salts with the desired mono-substituted products.

INTRODUCTION

The imidazole moiety is an important and frequent structural feature of many biologically active compounds such as cytochrome P450 enzyme inhibitors[1] and peptide analog inhibitors of human immunodeficiency virus (HIV-1) protease.[2] Most of imidazolode compounds are useful as drugs for treatment of many diseases, including cancer,[3] acquired immune deficiency syndrome (AIDS)[2] and also as cholesterol lowering[4] and antifungal agents. The steroids[5] consisted of an imidazole moiety at C-21 position are also intensively investigated for some special biological activity.[6,7] As a result, we planned to develop a new method for the synthesis of 1-substituted imidazoles from the corresponding α-bromoketone in improved yields without the formation of frequently observed 1,3-disubstituted imidazolium salts.

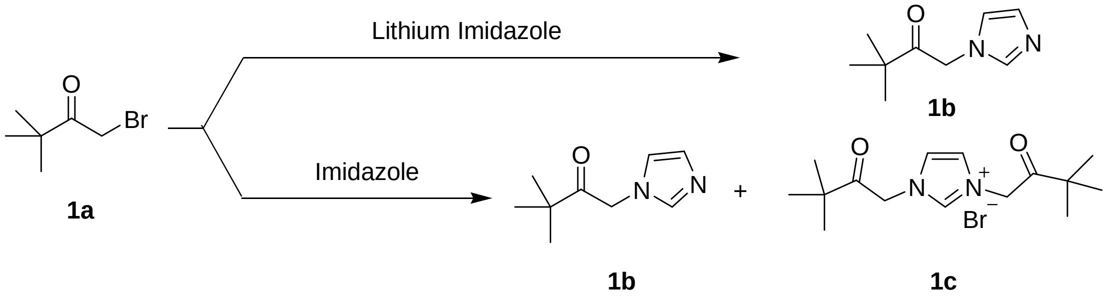
Many methods have been developed to prepare the 1-substituted imidazoles (monosubstituted imidazoles). Direct reaction of α-bromoketone with excess amount of imidazole[8] is a common method. In some cases, addition of a strong base or an acid catalyst was necessary.[9] Thermal decarboxylation of *N*-alkoxycarbonyl imidazoles[10] and the 1-protected imidazoles, such as 1-trimethylsilyl, 1-acetyl, 1-benzoyl and 1-ethoxycarbonylimidazole, was also reported.[11] Most of them could not provide satisfactory results due to the formation of 1,3-disubstituted imidazolium salts. The purification of 1-substituted imidazole derivatives was thus troublesome, especially in large-scale preparation. As a result, low isolated yields were the main disadvantage of these methods.

In this work, we reported an efficient and convenient method for the preparation of 1-substituted imidazoles from lithium imidazolide and α-bromoketones. The formation of 1,3-disubstituted products was not observed in this reaction. A control experiment was also performed by direct treatment of imidazole with α-bromoketones for the comparison purpose.

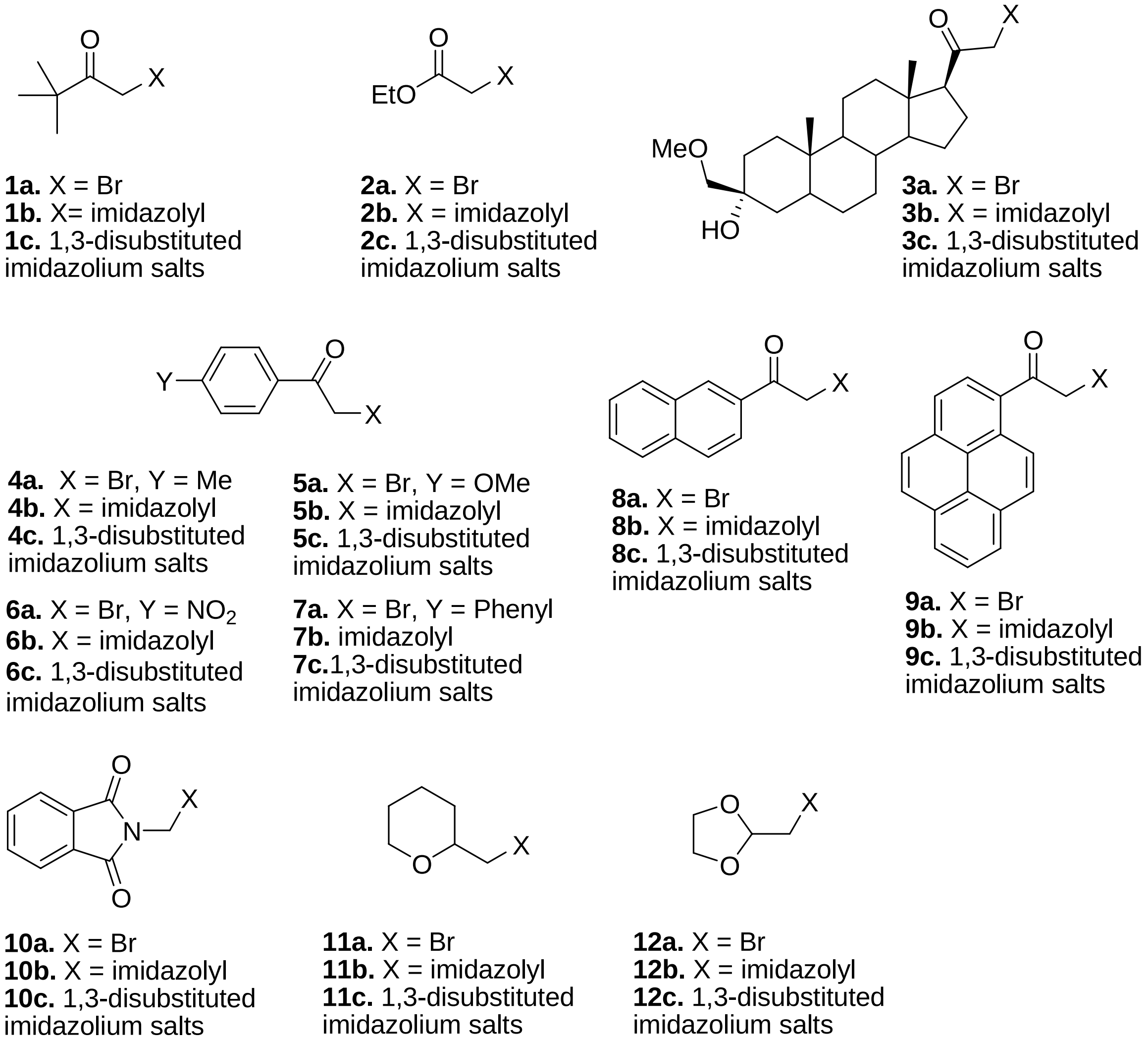
RESULTS AND DISCUSSION

The newly developed method for the synthesis of 1-substituted imidazoles was shown in Scheme 1. The preparation of lithium imidazolide was achieved by reaction of imidazole (3.0 equiv) in THF with lithium hydride (3.1 equiv) at reflux. α-Bromoketone (1.0 equiv) was the added to the reaction mixture at –5~0 °C for the generation of 1-substituted imidazoles. After normal workup and purification, the desired 1-substituted imidazoles were often isolated in solid form in 84–95% yields and no 1,3-disubstituted imidazolium salts were detected (see Scheme 1 and Table 1, **1b**–**9b**). The application of this method to *N*-(bromomethyl)phthalimide (**10a**) and 2-(bromomethyl)tetrahydro-2*H*-pyran (**11a**) also gave the corresponding products (**10b** and **11b**) in 85% and 75% yields without the formation of 1,3-disubstituted imidazolium salts (see Table 1).

Under the same conditions, bromoacetaldehyde ethylene acetal (**12a**) reacted with lithium imidazolide to give the mono-substituted products (**12b**) in 73% yield. The lower yields of **11a** and **12a** come from the weak stability of acetal and tetrahydropyran moieties for α-carbocation.[12]



Scheme 1



1a. X = Br
1b. X= imidazolyl
1c. 1,3-disubstituted imidazolium salts

2a. X = Br
2b. X = imidazolyl
2c. 1,3-disubstituted imidazolium salts

3a. X = Br
3b. X = imidazolyl
3c. 1,3-disubstituted imidazolium salts

4a. X = Br, Y = Me
4b. X = imidazolyl
4c. 1,3-disubstituted imidazolium salts

5a. X = Br, Y = OMe
5b. X = imidazolyl
5c. 1,3-disubstituted imidazolium salts

6a. X = Br, Y = NO_2
6b. X = imidazolyl
6c. 1,3-disubstituted imidazolium salts

7a. X = Br, Y = Phenyl
7b. imidazolyl
7c.1,3-disubstituted imidazolium salts

8a. X = Br
8b. X = imidazolyl
8c. 1,3-disubstituted imidazolium salts

9a. X = Br
9b. X = imidazolyl
9c. 1,3-disubstituted imidazolium salts

10a. X = Br
10b. X = imidazolyl
10c. 1,3-disubstituted imidazolium salts

11a. X = Br
11b. X = imidazolyl
11c. 1,3-disubstituted imidazolium salts

12a. X = Br
12b. X = imidazolyl
12c. 1,3-disubstituted imidazolium salts

Chart 1

In control experiments, α-bromoketones (**1a**–**10a**) were treated with the excess amount of imidazole by employing the published method.[8] However, the reaction gave a mixture of 1-substituted imidazoles and 1,3-disubstituted imidazolium salts (see Table 1). The yields of 1-substituted imidazoles by this method were thus lower than that by using lithium imidazolide as the reactant. Only in the case of 2-(bromomethyl)tetrahydro-2*H*-pyran (**11a**) and bromoacetaldehyde ethylene acetal (**12a**) gave the desired products exclusively (74% and 72% yields).The yields of the reactions in the control experiments were consistent with the data reported in literature.[13,14]

Table 1. α-Bromoketones and bromometyl compounds reacted with lithium imidazolide or imidazole.

Substrate	Lithium imidazolide		Imidazole				
	1-Substituted imidazoles	Yield (%)[a]	Reaction time (h)	Product			
				1-Substituted imidazoles	Yield (%)[a]	1,3-Disubstituted imidazolium salts	Yield (%)[a]
1a	**1b**	97	4	**1b**	30	**1c**	54
2a	**2b**	88	4	**2b**	40	**2c**	37
3a	**3b**	91	10	**3b**	45	**3c**	35
4a	**4b**	88	3	**4b**	43	**4c**	39
5a	**5b**	95	3	**5b**	40	**5c**	49
6a	**6b**	84	3	**6b**	31	**6c**	60
7a	**7b**	96	12	**7b**	37	**7c**	60
8a	**8b**	92	12	**8b**	32	**8c**	64
9a	**9b**	95	12	**9b**	34	**9c**	52
10a	**10b**	85	3	**10b**	39	**10c**	40
11a	**11b**	75	> 12	**11b**	74	**11c**	-[b]
12a	**12b**	73	> 12	**12b**	72	**12c**	-[b]

[a] The yield was provided by the column separation.
[b] Non-detectable.

This newly developed reaction proceeded in 0 °C and the reaction time was around 2.0 h, which was easily performed in laboratory and industry. The use of sodium imidazolide as the reactant was also tried and found to give the products in slightly lower yields compared with the use of lithium imidazolide. Nevertheless, the reaction gave more impurities and the preparation of sodium imidazolide required more attention. The new method was also applicable for large-scale synthesis and the undesired di-substituted by-products were also not formed. In example, compound (**3a**) could be prepared up to kilogram scale

(3.11 Kg of **3a**, see EXPERIMENTAL section) and column chromatography was not necessary.

The described method successfully provided a convenient and efficient preparation of 1-substituted imidazoles. The undesired di-substituted imidazole by-product was not found in this reaction. This method could also be applicable to large-scale industrial preparation of the 1-substituted imidazoles.

EXPERIMENTAL

All chemicals were reagent grade and used as purchased. All reactions were carried out under nitrogen atmosphere and monitored by TLC. Flash column chromatography was carried out on silica gel (230-400 mesh). Commercially available reagents were used without further purification unless otherwise noted. Ethyl acetate and hexanes were purchased from Mallinckrodt Chemical Co. Dry THF (reagent grade) was purchased from Aldrich. The following compounds were purchased from Aoros Chemical Co: 2-bromo-2-acetonaphinone, 1-(bromoacetyl)pyrene, α-bromo-4-methoxyacetophenone, α-bromo-4-methylacetophenone, 2-bromomethyl-1,3-dioxolane, *N*-bromomethylphthalimide, 2-bromomethyltetrahydro-2*H*-pyran, α-bromo-4-nitroacetophenone, 1-bromo-3,3-dimethylbutan-2-one, α -bromo-4-phenylacetophenone, ethyl 2-bromoacetate. Analytical thin-layer chromatography (TLC) was performed on precoated plates (silica gel 60 F-254), purchased from Merck Inc. Mixtures of AcOEt and hexane were used as eluants. Purification by gravity column chromatography was carried out by use of Merck Reagents Silica Gel 60 (particle size 0.063–0.200 mm, 70–230 mesh ASTM). Infrared (IR) spectra were measured on a Bomem Michelson Series FT-IR spectrometer. The wavenumbers reported are referenced to the polystyrene 1601 cm^{-1} absorption. Absorption intensities are recorded by the following abbreviations: s, strong; m, medium; w, weak. Proton NMR spectra were obtained on a Bruker (300 MHz) spectrometer by use of chloroform-*d*/ DMSO–d_6 as solvent. Carbon-13 NMR spectra were obtained on a Bruker (75 MHz) spectrometer by used of chloroform-*d* as solvent. Carbon-13 chemical shifts are referenced to the center of the $CDCl_3$ triplet (δ 77.0 ppm). Multiplicities are recorded by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; *J*, coupling constant (hertz). Elemental analyses were carried out on a Heraeus CHN–O RAPID element analyzer.

Standard procedure for the formation of 1-substituted imidazoles: A solution of imidazole (3.0 equiv) in THF was added with lithium hydride (3.1 equiv) and heated to reflux for 30 min under N_2. α-Bromoketones (**1a**–**9a**), *N*-(bromomethyl)phthalimide (**10a**), 2-(bromomethyl)tetrahydro-2*H*-pyran (**11a**), or bromoacetaldehyde ethylene acetal (**12a**, 1.0 equiv) in THF was slowly added to the reaction mixture at –5–0 °C for 5.0 min under N_2. After the reaction was completed, the reaction mixture was quenched and washed by a saturated NH_4Cl aqueous solution in ice-bath. The organic layer was concentrated under reduced pressure and the residue was purified by gravity column chromatography on silica gel or recrystallization to provide the desired 1-substituted imidazoles (**1b**–**12b**).

Compound (1b): TLC R_f 0.61 (10% MeOH in CH_2Cl_2); ^{1}H NMR (DMSO–d_6, 300 MHz) δ 1.16 (s, 9 H, 3 × CH_3), 5.22 (s, 2 H, CH_2), 6.86 (s, 1 H, imd-H), 6.97 (s, 1 H, imd-H), 7.46 (s, 1 H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 26.68, 43.51, 51.63, 121.52, 128.62, 139.03, 209.90; IR (diffuse reflectance) 3616 (m), 3114 (m), 2970 (s), 1719 (s, C=O), 1510 (m), 1479 (m), 1368 (m), 1290 (m), 1235 (m), 1064 (s), 1037 (m), 914 (m), 825 (m), 743 (m), 713 (m), 662 (m), 568 (m) cm^{-1}; FABMS *m/z* (relative intensity) 167 (M + 1, 100), 83 (3), 82 (13), 81 (8), 73 (11), 69 (11), 57 (16), 55 (3).

Compound (2b): TLC R_f 0.60 (10% MeOH in CH_2Cl_2); mp 121–123 °C; ^{1}H NMR (DMSO–d_6, 300 MHz) δ 1.13–1.22 (t, 3 H, J = 6.0 Hz, CH_3), 4.02–4.17 (q, 2 H, J = 6.0 Hz, OCH_2), 4.93 (s, 2 H, CH_2), 6.87 (s, 1 H, imd-H), 7.12 (s, 1 H, imd-H), 7.59 (s,1 H, imd-H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 14.41, 47.53, 61.46, 121.05, 128.47, 138.59, 168.95; IR (diffuse reflectance) 3117 (m), 2934 (m), 1681 (m, C=O), 1600 (m) 1574 (m), 1508 (m), 1459 (m), 1420 (m), 1359 (m), 1308 (m),1169 (m), 1111 (m), 991 (m), 907 (m), 836 (m), 818 (m), 793 (m), 718 (m) cm^{-1}; FABMS *m/z* (relative intensity) 155 (M + 1, 100), 154 (15), 137 (10), 136 (14), 127 (32), 107 (9), 95 (13), 91 (13), 83 (14), 81 (19), 77 (15), 71 (18), 67 (18).

Compound (3b): mp 196–198 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.66 (s, 3 H, 19-CH_3), 076 (s, 3 H, 18-CH_3), 0.78–1.05 (m, 2 H), 1.16–1.71 (m, 18 H), 1.92–1.97 (m, 1 H), 2.14–2.29 (m, 1 H), 2.57 (t, 3 H, J = 9.0 Hz, 17α-CH), 3.18 (s, 2 H, –OCH_2), 3.39 (s, 3 H, –OCH_3), 4.50 (d, 1 H, J = 18.0 Hz, –CHBr), 4.71 (d, 1 H, J = 18.0 Hz, –CHBr), 6.85 (s, 1 H), 7.09 (s, 1 H), 7.41 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 12.31, 13.88, 21.27, 23.25, 24.49, 28.54, 31.46, 31.98, 35.52, 35.54, 37.03, 38.12, 39.28, 44.84, 45.11, 54.14, 56.49, 56.78, 60.47, 71.06, 119.95, 129.41, 137.79, 203.19; IR (diffuse reflectance) 3483 (s), 2905 (s), 1754 (m, C=O), 1531 (m), 1446 (m), 1372 (m), 1265 (m), 1050 (m), 988 (m), 887 (m), 824 (m), 722 (m), 634 (m), 502 (m) cm^{-1}; MS *m/z* (relative intensity) 429 (M^+, 100), 427 (31), 413 (15), 411 (22), 383 (22), 137 (28), 105 (13), 93 (12), 82 (37), 69 (39); HRMS calcd for $C_{26}H_{40}N_2O_3$ 428.3039, found 428.3037.

Compound (4b): TLC R_f 0.38 (10% MeOH in CH_2Cl_2); mp 136–138 °C; ^{1}H NMR (DMSO–d_6, 300 MHz) δ 2.35 (s, 3 H), 5.69 (s, 2 H, CH_2), 6.91 (s, 1 H, imd-H), 7.10 (s, 1 H, imd-H), 7.39 (d, 2 H, J = 3.2 Hz, Ar-H), 7.57 (s, 1 H, imd-H), 7.93 (d, 2 H, J = 3.2 Hz, Ar-H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 21.65, 52.88, 121.37, 128.11, 128.47, 129.85, 132.37, 138.73, 144.86, 193.47; IR (diffuse reflectance) 3117 (m), 2933 (m), 1681 (m, C=O), 1603 (m), 1508 (m), 1441 (m), 1420 (m), 1348 (m), 1230 (m), 1110 (m), 991 (m), 907 (m), 816 (m), 793 (m), 718 (m) cm^{-1}; FABMS *m/z* (relative intensity) 201 (M + 1, 59), 147 (7), 131 (6), 119 (12), 117 (6), 115 (7), 105 (13), 91 (19), 83 (6), 79 (6), 77 (8), 71 (6), 69 (31), 67 (6).

Compound (5b): TLC R_f 0.31 (10% MeOH in CH_2Cl_2); mp 171–172 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.88 (s, 3 H, OCH_3), 5.33 (s, 2 H, CH_2), 6.93 (s, 1 H, imd-H), 6.97 (d, 2 H, J = 6.2 Hz, ArH), 7.11 (s, 1 H, imd-H), 7.51 (s, 1 H, imd-H), 7.94 (d, 2 H, *J* = 6.2 Hz, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 52.13, 55.57, 114.24, 120.33, 127.08, 129.12, 130.30, 138.10, 164.38, 189.98; IR (diffuse reflectance) 3397 (m), 2934 (m), 1687 (m, C=O), 1601 (m), 1509 (m), 1461 (m), 1350 (m), 1308 (m), 1260 (m), 1168 (m), 1081 (m), 1008 (m), 988 (m), 906 (m), 830 (m), 792 (m), 775 (m), 717 (m) cm^{-1}; FABMS *m/z* (relative intensity) 217 (M + 1, 100), 136 (19), 135 (47), 121 (39), 91 (21), 81 (23), 77 (32), 73 (21), 69 (42), 57 (44), 55 (43), 53 (10).

Compound (6b): TLC R_f 0.28 (10% MeOH in CH_2Cl_2); mp 164–166 °C; ^{1}H NMR (DMSO–d_6, 300 MHz) δ 5.79 (s, 2 H, CH_2), 6.92 (s, 1 H, imd-H), 7.11 (s, 1 H, imd-H), 7.58 (s, 1 H, imd-H), 8.24 (d, 2 H, *J* = 3.2 Hz, ArH), 8.39 (d, 2 H, *J* = 3.2 Hz, ArH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 53.48, 121.24, 123.70, 124.28, 127.37, 129.76, 130.78, 135.12, 193.12; IR (diffuse reflectance) 3040 (m), 1714 (s, C=O), 1600 (m), 1527 (m), 1355 (m), 1287 (m), 1106 (m), 1036 (m), 991 (m), 856 (m), 743 (m), 507 (m) cm^{-1}; FABMS *m/z* (relative intensity) 232 (M + 1, 51), 154 (40), 149 (24), 107 (27), 105 (20), 97 (26), 95 (32), 91 (35), 86 (100), 79 (25), 77 (26), 71 (27), 69 (67), 67 (33).

Compound (7b): TLC R_f 0.31 (6% MeOH in CH_2Cl_2); mp 195–197 °C; ^{1}H NMR (DMSO–d_6, 300 MHz) δ 5.77 (s, 2 H, CH_2), 6.92 (s, 1 H, imd-H), 7.13 (s, 1 H, imd-H), 7.34–7.55 (m, 3 H , ArH), 7.60 (s, 1 H, imd-H), 7.78 (d, 2 H, *J* = 3.1 Hz, Ar-H), 7.90 (d, 2 H, *J* = 3.1 Hz, ArH), 8.11 (d, 2 H, *J* = 3.1 Hz, ArH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 52.48, 120.81, 126.93, 127.77, 128.46, 128.61, 129.04, 129.51, 133.18, 138.24, 138.58, 145.05, 193.07; IR (diffuse reflectance) 3386 (m), 2933 (m), 1681 (m, C=O), 1601 (m), 1574 (m), 1441 (m), 1420 (m), 1358 (m), 1267 (m), 1170 (m), 1081 (m), 1039 (m), 991 (m), 907 (m), 834 (m), 818 (m), 743 (m), 719 (m) cm^{-1}; FABMS *m/z* (relative intensity) 263 (M + 1, 36), 181 (20), 154 (38), 137 (25), 136 (35), 91 (24), 90 (22), 89 (33), 81 (32), 79 (25), 78 (22), 77 (53), 73 (45), 71 (25).

Compound (8b): TLC R_f 0.43 (6% MeOH in CH_2Cl_2); mp 1226–228 °C; ^{1}H NMR (DMSO–d_6, 300 MHz) δ 5.90 (s, 2 H, CH_2), 6.97 (s, 1 H, imd-H), 7.19 (s, 1 H, imd-H), 7.67–7.75 (m, 3 H , ArH), 8.05–8.19 (m, 4 H , ArH), 8.81 (s, 1H, imd-H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 52.62, 120.95, 123.32, 127.19, 127.79, 127.90, 128.55, 128.98, 129.58, 130.01, 131.75, 132.09, 135.30, 138.38, 193.51; IR (diffuse reflectance) 3114 (m), 2922 (m), 1693 (s, C=O), 1505 (m), 1218 (m), 1187 (m), 1080 (m), 993 (m), 914 (m), 861 (m), 746 (m), 706 (m), 590 (m), 476 (m) cm^{-1}; FABMS *m/z* (relative intensity) 237 (M + 1, 27), 155 (60), 154 (100), 141 (27), 138 (35), 137 (61), 136 (93), 127 (29), 107 (38), 91 (32), 89 (41), 77 (49), 55 (48).

Compound (9b): TLC R_f 0.54 (10% MeOH in CH_2Cl_2); mp 279–281 °C; ^{1}H NMR (DMSO–d_6, 300 MHz) δ 5.94 (s, 2 H, CH_2), 7.00 (s, 1 H, imd-H), 7.28 (s, 1 H, imd-H), 7.83 (s, 1 H, imd-H), 8.13 (t, 1 H, *J* = 9.0 Hz, ArH), 8.24–8.43 (m, 7 H, ArH), 8.72 (d, 1 H, *J* = 3.0 Hz, ArH), 8.87 (d, 1 H, *J* = 3.0 Hz, ArH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 55.16, 121.44, 123.71, 124.45, 124.78, 126.78, 127.36, 127.56, 128.31, 129.39, 130.30, 130.99, 134.21, 138.88, 197.55; ; IR (diffuse reflectance) 3431 (m), 2930 (m), 1680 (m, C=O), 1594 (m), 1510 (m), 1384 (m), 1217 (m), 1122 (m), 994 (m), 847 (m), 757 (m) cm^{-1}; FABMS *m/z* (relative intensity) 311 (M + 1, 17), 229 (10), 215 (10), 201 (6), 155 (12), 154 (41), 138 (16), 137 (30), 136 (34), 107 (14), 91 (17), 89 (22), 81 (23), 77 (35), 71 (26).

Compound (10b): TLC R_f 0.45 (60% EtOAc in Hexane); mp 185–187 °C; ^{1}H NMR (DMSO–d_6, 300 MHz) δ 5.81 (s, 2 H, CH_2), 6.94 (s, 1 H, imd-H), 7.22 (s, 1 H, imd-H), 7.81 (s, 1 H, imd-H), 7.83–8.01 (m, 4 H , ArH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 47.38, 119.72, 124.03, 129.29, 131.53, 135.37, 138.05, 167.31; IR (diffuse reflectance) 2923 (m), 1716 (s, C=O), 1457 (m), 1117 (m), 1100 (m), 1030 (m), 952 (m), 822 (m), 664 (m), 530 (m) cm^{-1}; FABMS *m/z* (relative intensity) 228 (M + 1, 100), 227 (M$^+$, 4), 161 (8), 160 (66), 154 (10), 149 (5), 138 (5), 136 (11), 69 (9).

Compound (11b): TLC R_f 0.68 (8% MeOH in CH_2Cl_2); ^{1}H NMR (DMSO–d_6, 300 MHz) δ 1.21–1.79 (m, 6 H), 3.31–3.62 (m, 4 H), 3.87–3.96 (m, 1 H) 7.10 (s, 2H, imd-H), 7.82 (s, 1H, imd-H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 22.58, 25.30, 29.64, 37.11, 67.59, 76.22, 121.44, 135.11; IR (diffuse reflectance) 3366 (m), 3139 (m), 1593 (m), 1506 (m), 1258 (m), 1177 (m), 1047 (m), 986 (m), 838 (m), 757 (m), 632 (m) cm^{-1}; FABMS *m/z* (relative intensity) 167 (M + 1, 100), 137 (4), 82 (5), 81 (7), 69 (85), 67 (7), 57 (12), 55 (21).

Compound (12b): TLC R_f 0.60 (8% MeOH in CH_2Cl_2); ^{1}H NMR (DMSO–d_6, 300 MHz) δ 3.68 (t, 4 H , J = 6.0 Hz, OCH_2), 4.04 (d, 2 H, J = 3.0 Hz, CH_2), 4.98 (t, 1 H, J = 3.0 Hz, OCH), 6.77 (s, 1 H, imd-H), 7.02 (s, 1 H, imd-H), 7.47 (s, 1 H, imd-H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 48.80, 65.05, 101.68, 120.90, 128.38, 138.47; IR (diffuse reflectance) 3115 (m), 2894 (m), 1698 (m), 1506 (m), 1393 (m), 1287 (m), 1234 (m), 1143 (s), 1079 (m), 946 (m), 747 (m), 663 (m), 491 (m) cm^{-1}; FABMS *m/z* (relative intensity) 155 (M + 1, 31), 154 (33), 149 (40), 14 (60), 133 (56), 119 (56), 117 (78), 109 (52), 105 (60), 97 (54), 95 (82), 91 (79), 83 (73), 81 (100), 79 (69) , 77 (57).

The Scale-up procedure of 3α-Hydroxy-21-(1'-imidazolyl)-3β-methoxymethyl-5α-pregnan-20-one (3b): To a solution of imidazole (2.31 kg, 21.7 mol, 3.0 equiv) in THF (20 L) was added lithium hydride (0.179 kg, 22.4 mol, 3.1 equiv). The solution was heated at reflux for 30 min under N_2. Compound (**3a**) (3.11 kg, 7.28 mol, 1.0 equiv) in THF (10 L) was slowly added to the reaction mixture at –5–0 °C in a period of 0.5–1 h under N_2. The reaction solution was maintained at –5–0 °C and stirred for 2.0 h. When the reaction completed, the reaction mixture was quenched by saturated NH_4Cl aqueous solution (10 L) in ice-bath. The organic layer was separated and concentrated under reduced pressure to give pure **3b** (2.84 kg, 6.62 mol) as white powder in 91% isolated yield.

Standard procedure for the formation of 1-substituted imidazoles and 1,3-disubstituted

imidazolium salts: A solution of α-bromoketones (**1a**–**9a**, 1.0 equiv) or *N*-(bromomethyl)phthalimide (**10a**), 2-(bromomethyl)-tetrahydro-2*H*-pyran (**11a**, 1.0 equiv), or bromoacetaldehyde ethylene acetal (**12a**, 1.0 equiv) with imidazole (3.0 equiv) in THF was heated at reflux for 8–24 h under N_2. When the reaction was completed, the reaction mixture was concentrated to remove THF and the resulting oil was redissolved in CH_2Cl_2. The solution was washed with 5% aqueous $NaHCO_3$ solution and brine. The organic layer was dried over $MgSO_4$(s), filtered, and concentrated under reduced pressure. The residue was purified by gravity column chromatography on silica gel or recrystallization to provide the corresponding 1-substituted imidazoles (**1b**–**12b**) and 1,3-disubstituted imidazolium salt (**1c**–**10c**).

Compound (1c): TLC R_f 0.23 (10% MeOH in CH_2Cl_2); mp 81–82 °C; ^{1}H NMR (DMSO–d_6, 300 MHz) δ 1.19 (s, 18 H, 6 × CH_3), 5.74 (s, 4 H, 2 × CH_2), 7.71 (d, 2 H, J = 6.1 Hz, imd-H), 9.00 (s, 1 H, imd-H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 26.15, 43.04, 54.54, 121.52, 123.67, 138.63, 207.54; IR (diffuse reflectance) 3454 (m), 3144 (m), 3059 (m), 2970 (m), 1723 (s, C=O), 1563 (m), 1463 (m), 1368 (m), 1266 (m), 1176 (m), 1035 (m), 1009 (m), 940 (m), 839 (m), 781 (m), 628 (m), 580 (m) cm^{-1}; FABMS *m/z* (relative intensity) 266 (M + 1, 18), 265 (100), 180 (19), 167 (27), 154 (18), 137 (15), 136 (22), 107 (13), 95 (28), 91 (17), 85 (16), 83 (24), 81 (25), 79 (13).

Compound (2c): TLC R_f 0.17 (10% MeOH in CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δδ 1.25–1.30 (t, 6 H, J = 6.0 Hz, 2 × CH_3), 4.20–4.27 (q, 4 H, J = 6.0 Hz, 2 × OCH_2), 4.93 (s, 2 H, CH_2), 7.67 (d, 2 H, J = 9.2 Hz, imd-H), 9.88 (s, 1 H, imd-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.03, 50.49, 62.95, 123.45, 138.74, 166.12; IR (diffuse reflectance) 3392 (m), 2933 (m), 1728 (m, C=O), 1601 (m), 1508 (m), 1459 (m), 1376 (m), 1348 (m), 1169 (m), 1111 (m), 1021 (m), 992 (m), 877 (m), 828 (m), 818 (m), 793 (m), 718 (m) cm^{-1}; FABMS *m/z* (relative intensity) 256 (M + 1, 1), 255 (6), 241 (66), 213 (70), 185 (26), 168 (20), 155 (100), 127 (32), 81 (19), 69 (30).

Compound (3c): ^{1}H NMR ($CDCl_3$ + MeOD-d, 400 MHz) δ 0.66 (s, 6 H, 19-CH_3), 073 (s, 6 H, 18-CH_3), 0.75–1.09 (m, 4 H), 1.12–1.92 (m, 36 H), 2.01–2.23 (m, 4 H), 271 (t, 2 H, J = 8.8 Hz, 17-CH), 3.36 (s, 4 H, OCH_2), 3.36 (s, 6 H, OCH_3), 5.19 (d, 2 H, J = 18.4 Hz, CHBr), 5.49 (d, 2 H, J = 18.4 Hz, CHBr), 7.28 (s, 1 H), 7.32 (s, 1 H), 9.30 (s, 1 H); IR (diffuse reflectance) 3426 (s), 2931 (s), 1731 (m, C=O), 1632 (m), 1569 (m)1449 (m), 1385 (m), 1352 (m), 1294 (m), 1172 (m), 1119 (m), 1040 (m), 961 (m), 926 (m), 900 (m), 845 (m), 809 (m), 745 (m), 720 (m), 690 (m), 624 (m) cm^{-1}; MS *m/z* (relative intensity) 789 (M$^+$, 100), 773 (14), 744 (12), 673 (2), 605 (3), 551 (3), 497 (17), 429 (31), 442 (20), 383 (2), 315 (3), 281 (2), 207 (3), 149 (14), 137 (10), 81 (11), 73 (23), 69 (12); HRMS calcd for $C_{49}H_{77}N_2O_6$ 789.5776, found 789.5771.

Compound (4c): TLC R_f 0.15 (10% MeOH in CH_2Cl_2); mp 239–241 °C; ^{1}H NMR (DMSO–d_6, 300 MHz) δ 2.42 (s, 6 H, 2 × CH_3), 6.15 (s, 4 H, 2 × CH_2), 7.44 (d, 4H, J = 3.1 Hz, ArH), 7.80 (s, 2 H, imd-H), 7.97 (d, 4 H, J = 3.1 Hz, ArH), 9.10 (s, 1 H, imd-H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 21.73, 55.89, 124.10, 128.68, 130.03, 131.66, 138.97, 145.58, 191.21; IR (diffuse reflectance) 3393 (m), 3117 (m), 2933 (m), 1963 (m), 1728 (m, C=O), 1681 (m), 1573 (m), 1508 (m), 1441 (m), 1420 (m), 1358 (m), 1309 (m), 1169 (m), 1111 (m), 1021 (m), 992 (m), 877 (m), 828 (m), 793 (m), 775 (m), 718 (m) cm^{-1}; FABMS *m/z* (relative intensity) 334 (M + 1, 7), 333 (M^{+}, 29), 201 (7), 154 (28), 137 (21), 136 (29), 119 (29), 107 (21), 105 (25), 95 (26), 91 (33), 89 (22), 83 (27), 81 (32), 79 (22), 77 (32).

Compound (5c): TLC R_f 0.15 (10% MeOH in CH_2Cl_2); mp 258–260 °C; ^{1}H NMR (DMSO–d_6, 300 MHz) δ 3.87 (s, 6 H, 2 × OCH_3), 6.07 (s, 4 H, 2 × CH_2), 7.14 (d, 4H, *J* = 6.1 Hz, ArH), 7.75 (s, 2 H, imd-H), 8.03 (d, 4 H, *J* = 6.1 Hz, Ar-H), 9.05 (s, 1 H, imd-H); ^{13}C NMR (DMSO–d_6, 75 MHz) δ 56.06, 56.65, 115.23, 124.55, 127.43, 131.47, 139.47, 164.99, 190.40; IR (diffuse reflectance) 3460 (m), 3109 (m), 1723 (m, C=O), 1601 (m), 1573 (m), 1511 (m), 1467 (m), 1351 (m), 1309 (m), 1262 (m), 1218 (m), 1120 (m), 1089 (m), 1025 (m), 988 (m), 956 (m), 845 (m), 799 (m), 785 (m), 710 (m) cm^{-1}; FABMS *m/z* (relative intensity) 366 (M + 1, 9), 365 (M^{+}, 37), 230 (6), 217 (13), 215 (3), 176 (2), 169 (2), 168 (2), 167 (5), 166 (3), 165 (5), 164 (2), 163 (2).

Compound (6c): TLC R_f 0.15 (10% MeOH in CH_2Cl_2); mp 214–216 °C; ^{1}H NMR (DMSO–d_6, 300 MHz) δ 6.19 (s, 4 H, 2 × CH_2), 7.78 (s, 2 H, imd-H), 8.29 (d, 4 H, *J* = 2.9 Hz, ArH), 8.45 (d, 4 H, *J* = 2.9 Hz, ArH), 9.06 (s, 1 H, imd-H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 46.00, 120.23, 123.90, 124.22, 129.71, 130.89, 134.72, 190.9; IR (diffuse reflectance) 3371 (m), 3110 (m), 1704 (s, C=O), 1602 (m), 1519 (m), 1348 (m), 1176 (m), 1089 (m), 993 (m), 857 (m), 756 (m), 748 (m), 685 (m), 571 (m) cm^{-1}; FABMS *m/z* (relative intensity) 396 (M + 1, 2), 395 (M^{+}, 9), 245 (3), 222 (3), 191 (4), 185 (5), 154 (3), 149 (5), 136 (6), 107 (4), 102 (13), 97 (5), 91 (9), 89 (4).

Compound (7c): TLC R_f 0.12 (6% MeOH in CH_2Cl_2); mp 254–256 °C; ^{1}H NMR (DMSO–d_6, 300 MHz) δ 6.21 (s, 4 H, 2 × CH_2), 7.46–7.58 (m, 6 H, ArH), 7.82 (d, 2 H, *J* = 3.0 Hz, ArH), 7.83 (s, 1 H, imd-H), 7.99 (d, 4 H, *J* = 3.0 Hz, ArH), 8.18 (d, 4 H, *J* = 3.0 Hz, ArH), 9.14 (s, 1 H, imd-H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 56.07, 124.18, 127.51, 129.15, 129.34, 129.60, 132.98, 138.95, 139.03, 146.10, 191.32; IR (diffuse reflectance) 3349 (m), 3118 (m), 2933 (m), 1681 (m, C=O), 1601 (m), 1508 (m), 1459 (m), 1359 (m), 1309 (m), 1232 (m), 1111 (m), 1022 (m), 992 (m), 837 (m), 743 (m), 718 (m) cm^{-1}; FABMS *m/z* (relative intensity) 458 (M + 1, 35), 457 (100), 392 (7), 307 (16), 289 (11), 263 (7), 181 (13), 167 (19).

Compound (8c): TLC R_f 0.17 (6% MeOH in CH_2Cl_2); mp 261–263 °C; ^{1}H NMR (DMSO–d_6, 300 MHz) δ 6.30 (s, 4 H, 2 × CH_2), 7.67–7.77 (m, 4 H, ArH), 7.85 (s, 2 H, ArH), 8.05–8.21 (m, 8 H, ArH), 8.83 (s, 2 H, imd-H), 9.16 (s, 1 H, imd-H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 56.14, 123.68, 124.31, 127.90, 128.36, 129.27, 129.82, 130.13, 130.93, 131.52, 132.50, 135.99, 139.16, 191.69; IR (diffuse reflectance) 3439 (m), 3044 (m), 2956 (m), 1693 (m, C=O), 1455 (m), 1361 (m), 1171 (m), 1095 (m), 995 (m), 908 (m), 854 (m), 766 (m), 727 (m), 645 (m), 468 (m) cm^{-1}; FABMS *m/z* (relative intensity) 406 (M + 1, 3), 405

(M^+, 9), 391 (3), 237 (8), 167 (55), 155 (43), 154 (97), 149 (55), 138 (39), 137 (73), 136 (98), 107 (43), 91 (38), 89 (50), 77(60).

Compound (9c): TLC R_f 0.24 (10% MeOH in CH_2Cl_2); mp 329–331 °C; ^{1}H NMR (DMSO–d_6, 300 MHz) δ 6.53 (s, 4 H, 2 × CH_2), 8.09 (s, 2 H, imd-H), 8.16–8.51 (m, 16 H , ArH), 8.89 (d, 2 H, J = 5.8 Hz, ArH), 9.09 (d, 2 H, J = 5.8 Hz, ArH), 9.47 (s, 1 H, imd-H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 57.83, 123.52, 124.37, 124.62, 124.84, 126.97, 127.36, 127.49, 127.99, 129.81, 130.14, 130.58, 130.69, 130.88, 134.74, 194.43; IR (diffuse reflectance) 3384 (m), 3043 (m), 1682 (m, C=O), 1593 (m), 1508 (m), 1382 (m), 1221 (m), 1121 (m), 961 (m), 849 (m), 761 (m), 718 (m) cm^{-1}; FABMS *m/z* (relative intensity) 556 (M + 1, 7), 555 (13), 554 (55), 553 (100), 391 (29), 311 (30), 307 (51), 289 (39), 229 (41), 215 (74), 202 (26), 201 (33).

Compound (10c): TLC R_f 0.10 (60% EtOAc in Hexane); mp 297–299 °C; ^{1}H NMR (DMSO–d_6, 300 MHz) δ 6.01 (s, 4 H, 2 × CH_2), 7.78 (s, 2 H, imd-H), 7.89–7.98 (m, 8 H , ArH), 9.42 (s, 1 H, imd-H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 50.06, 122.95, 124.21, 131.77, 135.54, 137.85, 167.09; IR (diffuse reflectance) 3457 (m), 1723 (s, C=O), 1544 (m), 1469 (m), 1355 (m), 1292 (m), 1146 (m), 1024 (m), 955 (m), 853 (m), 710 (m) cm^{-1}; FABMS *m/z* (relative intensity) 388 (M + 1, 2), 387 (M^+, 8), 229 (15), 228 (100), 161 (11), 160 (89), 154 (17), 149 (8).

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