

HETEROCYCLES, Vol. 68, No. 7, 2006, pp. 1359 - 1370. © The Japan Institute of Heterocyclic Chemistry
Received, 10th March, 2006, Accepted, 29th May, 2006, Published online, 30th May, 2006. COM-06-10726

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

Chun Min Lin,^c Fung Fuh Wong,^{*,a,b} Jiann-Jyh Huang,^d and Mou-Yung
Yeh^{c,e}

^aSustainable Environment Research Center, National Cheng Kung University, No. 500, Sec. 3, An-ming Rd., Tainan City, Taiwan 709, R.O.C.

^bGraduate Institute of Pharmaceutical Chemistry, China Medical University, No. 91 Hsueh-Shih Rd. Taichung, Taiwan 40402, R.O.C.

^cDepartment of Chemistry, National Cheng Kung University, No. 1, Ta Hsueh Rd., Tainan, Taiwan 70101, R.O.C.

^dDevelopment Center for Biotechnology, No. 101, Lane 169, Kangning St., Xizhi City, Taipei County, Taiwan 221, R.O.C.

^eNan Jeon Institute of Technology, No.178, Chaocin Rd., Yanshuei Township, Tainan County, Taiwan 737, R. O. C.

*Corresponding Author. Tel.: +886 6 384 0136 ext. 212; Fax.: +886 6 384 0960.
E-mail address: wongungfuh@yahoo.com.tw (F. F. Wong).

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 inhibitors¹ and peptide analog inhibitors of human immunodeficiency virus (HIV-1) protease.² Most of imidazole compounds are useful as drugs for

treatment of many diseases, including cancer,³ acquired immune deficiency syndrome (AIDS)² and also as cholesterol lowering⁴ and antifungal agents. The steroids⁵ 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.

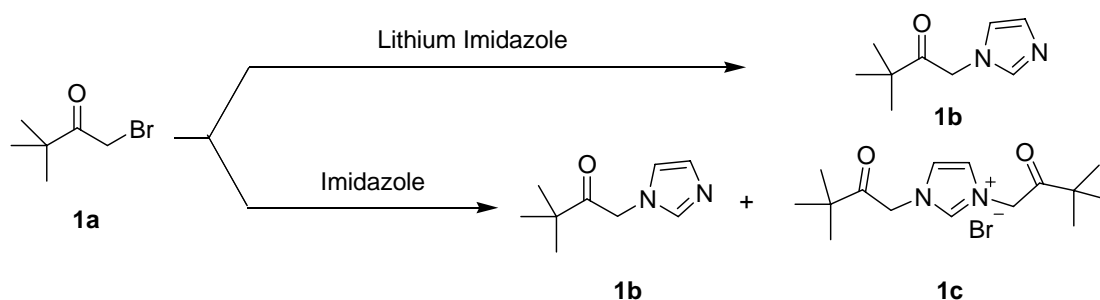
Many methods have been developed to prepare the 1-substituted imidazoles (monosubstituted imidazoles). Direct reaction of α -bromoketone with excess amount of imidazole⁸ is a common method. In some cases, addition of a strong base or an acid catalyst was necessary.⁹ Thermal decarboxylation of *N*-alkoxycarbonyl imidazoles¹⁰ 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 added to the reaction mixture at $-5\sim 0$ °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

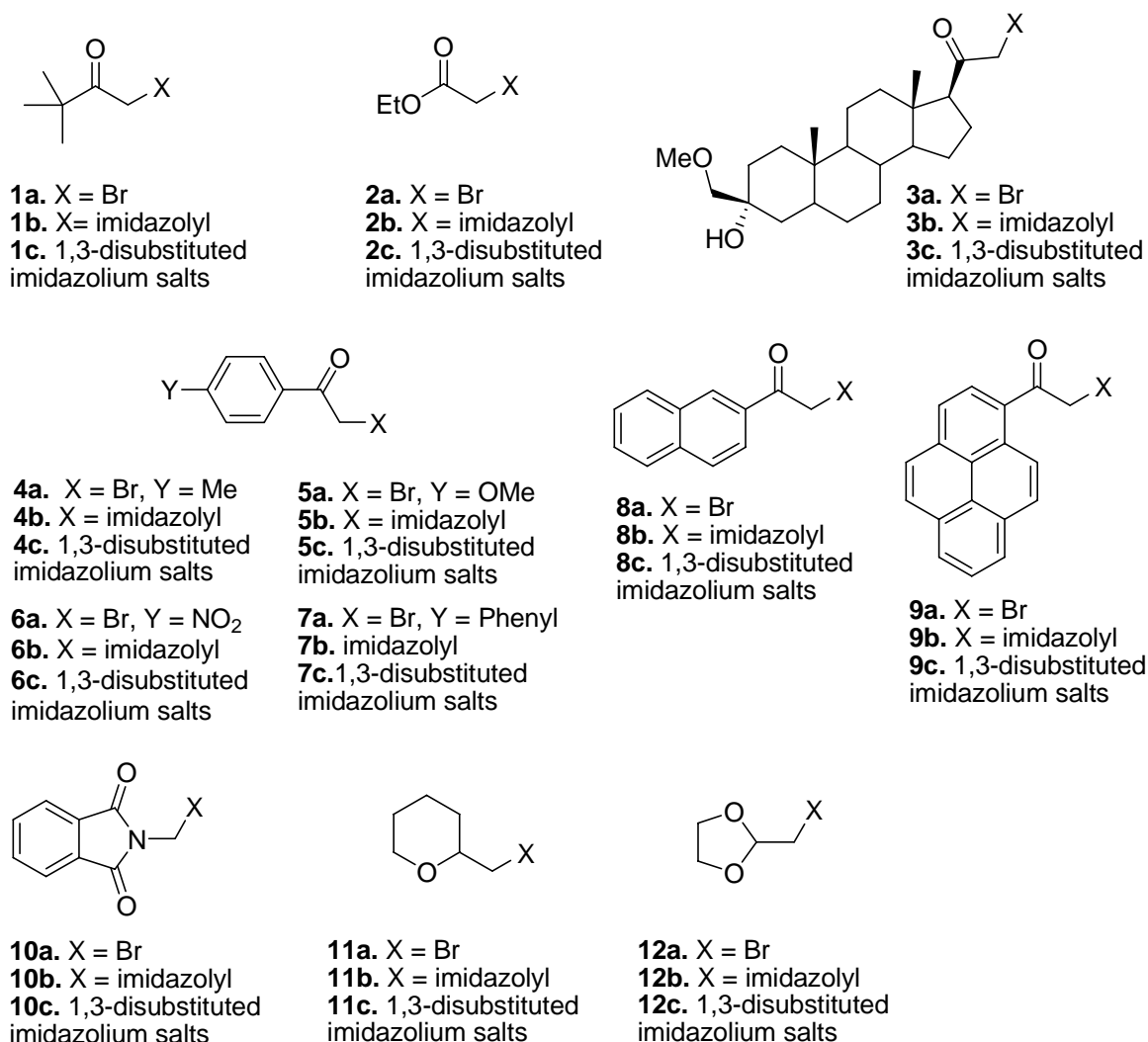


Chart 1

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 bromomethyl compounds reacted with lithium imidazolidate or imidazole.

| Substrate | Lithium imidazolidate | | | Imidazole | | | |
|------------|--------------------------|------------------------|-------------------|--------------------------|------------------------|--|------------------------|
| | 1-Substituted imidazoles | Yield (%) ^a | Reaction time (h) | 1-Substituted imidazoles | Yield (%) ^a | Product 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 |

^aThe yield was provided by the column separation.

^bNon-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 imidazolidate as the reactant was also tried and found to give the products in slightly lower yields compared with the use of lithium imidazolidate. Nevertheless, the reaction gave more impurities and the preparation of sodium imidazolidate 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 use of chloroform-*d* as solvent. Carbon-13 chemical shifts are referenced to the center of the CDCl₃ 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 N₂. 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 N₂. After the reaction was completed, the reaction mixture was quenched and washed by a saturated NH₄Cl 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); ^1H NMR ($\text{DMSO}-d_6$, 300 MHz) δ 1.16 (s, 9 H, $3 \times \text{CH}_3$), 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 ($\text{DMSO}-d_6$, 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; ^1H NMR ($\text{DMSO}-d_6$, 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 ($\text{DMSO}-d_6$, 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; ^1H NMR (CDCl_3 , 400 MHz) δ 0.66 (s, 3 H, 19- CH_3), 0.76 (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, 17 α -CH), 3.18 (s, 2 H, $-\text{OCH}_2$), 3.39 (s, 3 H, $-\text{OCH}_3$), 4.50 (d, 1 H, $J = 18.0$ Hz, $-\text{CHBr}$), 4.71 (d, 1 H, $J = 18.0$ Hz, $-\text{CHBr}$), 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 $\text{C}_{26}\text{H}_{40}\text{N}_2\text{O}_3$ 428.3039, found 428.3037.

Compound (4b): TLC R_f 0.38 (10% MeOH in CH_2Cl_2); mp 136–138 °C; ^1H NMR ($\text{DMSO}-d_6$, 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 ($\text{DMSO}-d_6$, 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; ^1H 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; ^1H NMR ($\text{DMSO}-d_6$, 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 ($\text{DMSO}-d_6$, 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; ^1H NMR ($\text{DMSO}-d_6$, 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 ($\text{DMSO}-d_6$, 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; ^1H NMR ($\text{DMSO}-d_6$, 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 ($\text{DMSO}-d_6$, 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; ^1H NMR ($\text{DMSO}-d_6$, 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 ($\text{DMSO}-d_6$, 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; ^1H NMR (DMSO- d_6 , 300 MHz) δ 5.81 (s, 2 H, CH₂), 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 CH₂Cl₂); ^1H 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 CH₂Cl₂); ^1H NMR (DMSO- d_6 , 300 MHz) δ 3.68 (t, 4 H, J = 6.0 Hz, OCH₂), 4.04 (d, 2 H, J = 3.0 Hz, CH₂), 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 3 α -Hydroxy-21-(1'-imidazolyl)-3 β -methoxymethyl-5 α -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 N₂. 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 N₂. 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 NH₄Cl 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 N₂. When the reaction was completed, the reaction mixture was concentrated to remove THF and the resulting oil was redissolved in CH₂Cl₂. The solution was washed with 5% aqueous NaHCO₃ solution and brine. The organic layer was dried over MgSO₄(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 CH₂Cl₂); mp 81–82 °C; ¹H NMR (DMSO-*d*₆, 300 MHz) δ 1.19 (s, 18 H, 6 \times CH₃), 5.74 (s, 4 H, 2 \times CH₂), 7.71 (d, 2 H, *J* = 6.1 Hz, imd-H), 9.00 (s, 1 H, imd-H); ¹³C 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 CH₂Cl₂); ¹H NMR (CDCl₃, 300 MHz) δ 1.25–1.30 (t, 6 H, *J* = 6.0 Hz, 2 \times CH₃), 4.20–4.27 (q, 4 H, *J* = 6.0 Hz, 2 \times OCH₂), 4.93 (s, 2 H, CH₂), 7.67 (d, 2 H, *J* = 9.2 Hz, imd-H), 9.88 (s, 1 H, imd-H); ¹³C NMR (CDCl₃, 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): ¹H NMR (CDCl₃ + MeOD-*d*, 400 MHz) δ 0.66 (s, 6 H, 19-CH₃), 0.73 (s, 6 H, 18-CH₃), 0.75–1.09 (m, 4 H), 1.12–1.92 (m, 36 H), 2.01–2.23 (m, 4 H), 2.71 (t, 2 H, *J* = 8.8 Hz, 17-CH), 3.36 (s, 4 H, OCH₂), 3.36 (s, 6 H, OCH₃), 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 C₄₉H₇₇N₂O₆ 789.5776, found 789.5771.

Compound (4c): TLC *R_f* 0.15 (10% MeOH in CH₂Cl₂); mp 239–241 °C; ¹H NMR (DMSO-*d*₆, 300 MHz) δ 2.42 (s, 6 H, 2 \times CH₃), 6.15 (s, 4 H, 2 \times CH₂), 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); ¹³C 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; ^1H NMR (DMSO- d_6 , 300 MHz) δ 3.87 (s, 6 H, 2 \times OCH₃), 6.07 (s, 4 H, 2 \times CH₂), 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; ^1H NMR (DMSO- d_6 , 300 MHz) δ 6.19 (s, 4 H, 2 \times CH₂), 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; ^1H NMR (DMSO- d_6 , 300 MHz) δ 6.21 (s, 4 H, 2 \times CH₂), 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; ^1H NMR (DMSO- d_6 , 300 MHz) δ 6.30 (s, 4 H, 2 \times CH₂), 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 CH₂Cl₂); mp 329–331 °C; ¹H NMR (DMSO-*d*₆, 300 MHz) δ 6.53 (s, 4 H, 2 × CH₂), 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); ¹³C 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; ¹H NMR (DMSO-*d*₆, 300 MHz) δ 6.01 (s, 4 H, 2 × CH₂), 7.78 (s, 2 H, imd-H), 7.89–7.98 (m, 8 H, ArH), 9.42 (s, 1 H, imd-H); ¹³C 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).

ACKNOWLEDGEMENTS

We are grateful to the National Science Council of Republic of China for financial support.

REFERENCES

- 1 H. Vanden Bossche, *J. Steroid Biochem. Molec. Biol.*, 1992, **42**, 45.
- 2 S. K. Thompson, K. H. M. Murthy, B. Zhao, E. Winborne, D. W. Green, S. M. Fisher, R. L. DesJarlais, T. A. Jr. Tomaszek, T. D. Meek, J. G. Gleason, and S. S. Abdel-Meguid, *J. Med. Chem.*, 1994, **37**, 3100.
- 3 (a) F. T. Boyle and G. F. Costello, *Chem. Soc. Rev.*, 1998, **27**, 251. (b) V. C. O. Njar and A. M. H. Brodie, *Drugs*, 1999, **58**, 233.
- 4 D. H. Blackenhorn, S. A. Nission, R. L. Johnson, M. E. Sanmarco, S. P. Azen, and L. Cashin-Hemphill, *J. Am. Med. Assoc.*, 1987, **257**, 3233.
- 5 R. Howe, *Adv. Drug Res.*, 1974, **9**, 7.
- 6 V. C. O. Njar, *Synthesis*, 2000, **14**, 2019.
- 7 F. F. Wong, C.-Y. Chen, T.-H. Chen, J.-J. Huang, H.-P. Fang, and M.-Y. Yeh, *Steroids*, 2006, **71**, 77.

- 8 (a) C. D. Jones, M. A. Winter, K. S. Hirsch, N. Stamm, H. M. Talyor, H. E. Holden, J. D. Davenport, E. V. Krumkalns, and R. G. Suhr, *J. Med. Chem.*, 1990, **33**, 416. (b) D. M. Rotstein, D. J. Kertesz, K. A. M. Walker, and D. C. Swinney, *J. Med. Chem.*, 1992, **35**, 2818.
- 9 (a) M. R. Grimmett, In *Advances in Hteterocyclic Chemistry*; Vol. 12, ed. by A. R. Katritzky and A. J. Boulton, Academic Press, New York, 1970, pp. 162–166. (b) M. Häring, *Helev. Chim. Acta*, 1959, **42**, 1845. (c) Sankyo, Japan Kokai 51-105060. *Chem. Abstr.*, 1977, **86**, 155649t.
- 10 K. Yamauchi and M. Kinoshita, *J. Chem. Soc., Perkin Trans. I.*, 1973, 2506.
- 11 T. Kamijo, Y. Yamamoto, H. Harada, and K. Iizuka, *Chem. Pharm. Bull.*, 1983, **31**, 1213.
- 12 H. J. J. Loozen, J. J. M. Drouen, and O. Piepers, *J. Org. Chem.*, 1975, **40**, 3279.
- 13 J. Heeres and J. V. Cutsem, *J. Med. Chem.*, 1981, **24**, 1360.
- 14 J. G. Cannon, M. F. Sahin, R. K. Bhatnagar, J. R. Flynn, and J. P. Long, *J. Med. Chem.*, 1991, **34**, 1582.