

Regioselective Alkylation of 2-Alkyl-5,6,7,8-tetrahydro-3H-cycloheptimidazol-4-ones and 2-Alkyl-3H-cycloheptimidazol-4-ones

Motoharu SONEGAWA,* Masayuki YOKOTA, Hiroshi TOMIYAMA, and Tsuyoshi TOMIYAMA

Kotobuki Research Laboratories, Kotobuki Seiyaku Company, Ltd.; 6351 Sakaki-Machi, Nagano 389–0697, Japan.

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Regioselective alkylation of 2-alkyl-5,6,7,8-tetrahydro-3H-cycloheptimidazol-4-one (**1**) and 2-alkyl-3H-cycloheptimidazol-4-one (**2**) was investigated. 3-[2'-(1-*tert*-Butyl-1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-2-propyl-5,6,7,8-tetrahydro-1H-cycloheptimidazol-4-one (**6**) was preferentially obtained under the conditions by using NaH in DMF or THF. On the other hand, 3-[2'-(1-*tert*-butyl-1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-2-propyl-5,6,7,8-tetrahydro-3H-cycloheptimidazol-4-one (**5**), the synthetic intermediate compound of Pratosartan, was obtained selectively in the presence of *n*-Bu₄NBr in toluene by using aqueous sodium hydroxide as a base. In this reaction, it was found that the concentration of the alkaline solution influences its regioselectivity. This selectivity was observed even for aldehyde and ester derivatives.

Key words regioselective alkylation; phase transfer catalyst; cycloheptimidazol-4-one; 4-acylimidazole; angiotensin receptor antagonist; Pratosartan

Recently, extremely useful imidazole derivatives such as Losartan,¹⁾ Candesartan,²⁾ Olmesartan³⁾ have been developed as angiotensin-II (AII) receptor antagonists. We have reported that Pratosartan⁴⁾ was an AT₁ selective AII receptor antagonist having a new structure including a 7-membered ring ketone and KT3-866⁵⁾ was a more strong AT₁ selective AII receptor antagonist that arranged a carboxymethylidene moiety connected to the 7-membered ring. These AII receptor antagonists contain an *N*-alkyl imidazole core as a common structural unit.

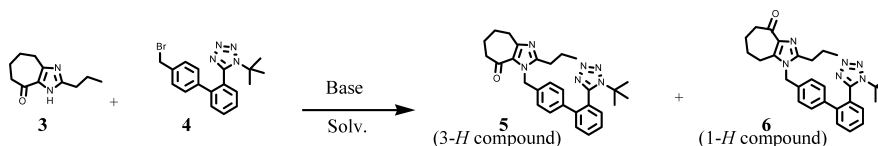
N-Alkylation to the substituted imidazoles gives the desired product and its regioisomer. Therefore, regioselective *N*-alkylation to the substituted imidazoles was examined to synthesize these compounds. The replacement at the N3 position of the imidazole derivative took place with high regioselectivity in the reaction of 4-acylimidazole and benzyl halide in the presence of K₂CO₃ in *N,N*-dimethylformamide (DMF) or *N,N*-dimethylacetamide (DMA).^{6,7)} Also, it has been reported that 4-formylimidazole gives the 3*N*-alkylated compounds in high selectivity by using phase transfer cata-

lyst (PTC).⁸⁾ We examined regioselective *N*-alkylation to the cycloheptimidazol-4-one compounds for the synthesis of industrial-scale Pratosartan. In this paper, we report the details in the alkylation reactions of cycloheptimidazol-4-one compounds or 4-acylimidazole compounds with alkyl halides in the presence of a PTC.

Results and Discussion

The reactions of 2-propyl-5,6,7,8-tetrahydro-3H-cycloheptimidazol-4-one (**3**)⁹⁾ and 5-(4'-bromomethyl-biphenyl-2-yl)-1-*tert*-butyl-1H-tetrazole (**4**) under the general *N*-alkylation conditions were carried out. The yield and regioselectivity are shown in Table 1. Compound (**6**) was obtained as a major product in DMF or tetrahydrofuran (THF) as a solvent by using NaH (Table 1, entries 1, 2). Similarly, under the K₂CO₃/DMF reaction conditions as a representative method for the imidazole alkylation, compound (**5**) was obtained as a major product (Table 1, entry 3). Interestingly, the reactions with *t*-BuOK³⁾ resulted in reversed regioselectivity between DMF and THF (Table 1, entries 5, 6). The use of 1,8-diazabi-

Table 1. Reaction of 2-Propyl-5,6,7,8-tetrahydro-3H-cycloheptimidazol-4-one (**3**) with 5-(4'-Bromomethyl-biphenyl-2-yl)-1-*tert*-butyl-1H-tetrazole (**4**)



Entry	Base	Solvent	Reaction time (h)	Yield ^{a)} (%)	Selectivity ^{b)} 5/6
1	NaH	DMF	1	98	28/72
2	NaH	THF	2	97	24/76
3	K ₂ CO ₃	DMF	6	97	76/24
4	K ₂ CO ₃ , 18-Crown-6	THF	16	95	71/29
5	<i>t</i> -BuOK	DMF	1.5	95	74/26
6	<i>t</i> -BuOK	THF	8	96	34/66
7	DBU	DMF	5	35	88/12
8	DBU	THF	16	24	87/13
9	10% NaOH, <i>n</i> -Bu ₄ NBr (0.4 eq)	DMF	1	85	56/44
10	10% NaOH, <i>n</i> -Bu ₄ NBr (0.4 eq)	THF	2	94	85/15

a) Total isolated yield of compound (**5**) and compound (**6**) is shown. b) Calculated ratio based on isolated yields of compound (**5**) and compound (**6**).

cyclo[5.4.0]-7-undecene (DBU) showed excellent selectivity, but yields were low due to the heterogeneous reactions by formation of an insoluble lump (Table 1, entries 7, 8). Interestingly, the reaction conditions (*n*-Bu₄NBr/10% aq. NaOH) showed poor selectivity in DMF, whereas high selectivity was obtained in THF (Table 1, entries 9, 10). Since the high yield and the high regioselectivity were obtained, we examined the further effect of PTC under this biphasic reaction conditions.

Owing to a difference in the selectivity that was observed between DMF and THF, the effects of solvents were examined (Table 2). The relatively high selectivity at *N*3-alkylation around 80% to 90% yields was obtained even in CHCl₃, CH₃COCH₃, CH₃CN. Although similar selectivity was observed in alcohol solvents, longer reaction time was required, and the yield was low. The best results were obtained in the *N*3-alkylation in toluene or similar aromatic solvents with high selectivity (*ca.* 91%) and the highest yield (*ca.* 95%). Therefore, the finally obtained conditions with the combination of aq. NaOH/PTC/toluene should be the best procedure in industrial-scale.

Next, a series of PTC of various kinds of alkyl groups in the size and the kinds of the counter anion was examined (Table 3). The difference in the counter anion of PTC had no

effect on the yield and regioselectivity. On the other hand, the difference in the length of the alkyl group influenced clearly the reaction time, resulting in tetra-*n*-octylammonium bromide (*n*-Oct₄NBr, Table 3, entry 8) with much shorter reaction time (0.5 h). On the contrary, tetra-*n*-propylammonium bromide (*n*-Pr₄NBr, Table 3, entry 6) with a shorter alkyl group needed longer reaction time (8 h). Furthermore, the reaction did not complete even after 40 h in the case of tetraethylammonium bromide (Et₄NBr, Table 3, entry 5). The difference in this reaction time is attributed to the difference of the movement ability to the organic layer by PTC, of which observation could be obtained by NMR measurement of the catalyst. The phosphonium salt also gave similar regioselectivity to ammonium salt (Table 3, entry 9).

The concentration of the alkaline aqueous solution as one factor must be examined (Table 4). As the result, higher regioselectivity was observed in lower alkaline concentration for all alkali-metal hydroxides. On the other hand, higher alkaline concentration shortens the reaction time, but the selectivity of the products was decreased. Therefore, it is considered that the best reaction conditions would be to use relatively low alkaline concentration in spite of a slight loss of the yield.

The reversed phenomenon was observed in the alkylation of 2-propyl-3*H*-cycloheptimidazol-4-one (**7**) that is the con-

Table 2. Effect of Solvent

$$3 + 4 \xrightarrow[\text{Solvent, r.t.}]{10\% \text{ aq. NaOH, } n\text{-Bu}_4\text{NBr (0.4 eq.)}} 5 + 6$$

Entry	Solvent	Reaction time (h)	Yield ^{a)} (%)	Selectivity ^{b)} 5/6
1	DMF	1	85	56/44
2	THF	2	94	85/15
3	CHCl ₃	1	87	82/18
4	CH ₃ COCH ₃	0.5	93	79/21
5	CH ₃ CN	1	93	79/21
6	EtOH	24	53	81/19
7	<i>n</i> -BuOH	18	76	89/11
8	Benzene	4	95	90/10
9	Toluene	4	94	91/9
10	<i>o</i> -Xylene	4	94	90/10

a) Total isolated yield of compound (**5**) and compound (**6**) is shown. b) Calculated ratio based on isolated yields of compound (**5**) and compound (**6**).

Table 3. Effect of Phase Transfer Catalyst

$$3 + 4 \xrightarrow[\text{Toluene}]{10\% \text{ aq. NaOH, PTC (0.4 eq.)}} 5 + 6$$

Entry	PTC	Reaction time (h)	Yield ^{a)} (%)	Selectivity ^{b)} 5/6
1	<i>n</i> -Bu ₄ NCl	4	94	91/9
2	<i>n</i> -Bu ₄ NBr	4	94	91/9
3	<i>n</i> -Bu ₄ NI	4	94	91/9
4	<i>n</i> -Bu ₄ NHSO ₄	4	94	91/9
5	<i>n</i> -Et ₄ NBr	40	64	85/15
6	<i>n</i> -Pr ₄ NBr	8	92	92/8
7	<i>n</i> -Hex ₄ NBr	1	95	90/10
8	<i>n</i> -Oct ₄ NBr	0.5	95	91/9
9	<i>n</i> -Bu ₄ PBr	4	94	89/11

a) Total isolated yield of compound (**5**) and compound (**6**) is shown. b) Calculated ratio based on isolated yields of compound (**5**) and compound (**6**).

Table 4. Effect of Aqueous Alkaline Solution

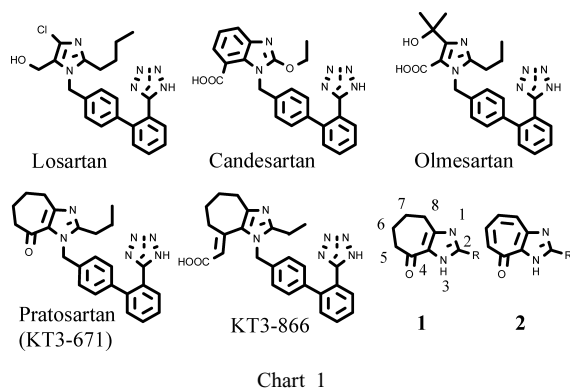
$$3 + 4 \xrightarrow[\text{in toluene}]{\text{Base, } n\text{-Bu}_4\text{NBr (0.4 eq.)}} 5 + 6$$

Entry	Base	Temp. (°C)	Reaction time (h)	Yield ^{a)} (%)	Selectivity ^{b)} 5/6
1	5% aq. NaOH	r.t.–45	22 ^{c)}	94	96/4
2	10% aq. NaOH	r.t.	4	94	91/9
3	20% aq. NaOH	r.t.	2	95	88/12
4	5% aq. KOH	r.t.–45	22 ^{c)}	94	96/4
5	10% aq. KOH	r.t.	10	94	92/8
6	20% aq. KOH	r.t.	3	95	89/10
7	5% aq. LiOH	r.t.–45	22 ^{c)}	84	94/6
8	10% aq. LiOH	r.t.	8	94	83/17

a) Total isolated yield of compound (**5**) and compound (**6**) is shown. b) Calculated ratio based on isolated yields of compound (**5**) and compound (**6**). c) Reaction was carried out at room temperature for 18 h and then at 45 °C for 4 h.

jugate unsaturated 7-membered ring ketone (Table 5). In the reactions to compound (7), higher selectivity was observed in higher alkaline concentration. Cycloheptimidazol-4-ones having a tautomer with 10π electron plane structure may stabilize metal chelation between the *N*3 atom and the 4-carbonyl group (Chart 2).¹⁰ Therefore, the reaction proceeds much more easily in the *N*3-alkylation with high selectivity.

Based on the fundamental data mentioned above, we suc-



ceeded in the production of the 3-[2'-(1-*tert*-butyl-1*H*-tetrazol-5-yl)-biphenyl-4-ylmethyl]-2-propyl-3*H*-cycloheptimidazol-4-one (8) in several dozens kilogram-scale by utilizing the reaction system of aq. NaOH/PTC/toluene, resulting in highly pure Pratosartan.

Application of the present method to other imidazole compounds such as 4-acylimidazoles was investigated. In the case of aldehyde or ester, the *N*3-alkylated compound was given mainly with 2 : 1 selectivity and there is a certain tendency for increasing the selectivity with the bulkiness of the imidazole compounds (10b, d, f, h). A 6-membered ring ketone derivative (10i)¹⁵ showed similar regioselectivity to compound (3). In contrast, clear selectivity was not observed in the non-cyclic ketone (10j) similar to 4-methyl imidazole.

Conclusion

In conclusion, the regioselective alkylation to 2-propyl-

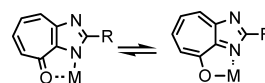
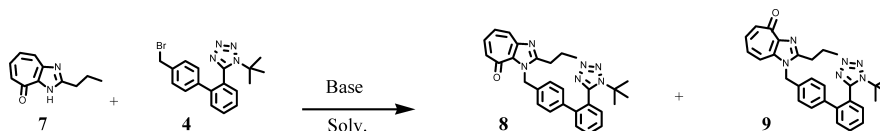


Chart 2. Tautomeric Structure of Cycloheptimidazol-4-one

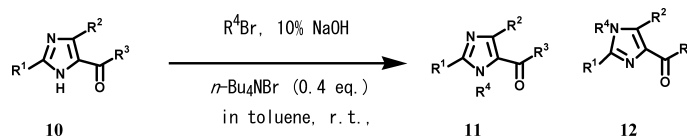
Table 5. Reaction of 2-Propyl-3*H*-cycloheptimidazol-4-one (7) with 5-(4'-Bromomethyl-biphenyl-2-yl)-1-*tert*-butyl-1*H*-tetrazole (4)



Entry	Base, PTC	Solvent	Temp. (°C)	Reaction time (h)	Yield ^{a)} (%)	Selectivity ^{b)} 8/9
1	NaH	DMF	r.t.	2	95	16/84
2	K ₂ CO ₃	DMF	r.t.	4	92	87/13
3	<i>t</i> -BuOK	DMF	r.t.	4	87	86/14
4	10% aq. NaOH, <i>n</i> -Bu ₄ NBr	Toluene	45	9	94	92/8
5	20% aq. NaOH, <i>n</i> -Bu ₄ NBr	Toluene	45	4	94	94/6
6	30% aq. NaOH, <i>n</i> -Bu ₄ NBr	Toluene	45	3.5	94	94/6
7	40% aq. NaOH, <i>n</i> -Bu ₄ NBr	Toluene	45	3	94	95/5
8	30% aq. NaOH, <i>n</i> -Bu ₄ NBr	Toluene	r.t.–45	22 ^{c)}	90	98/2

^{a)} Total isolated yield of compound (8) and compound (9) is shown. ^{b)} Calculated ratio based on isolated yields of compound (8) and compound (9). ^{c)} Reaction was carried out at room temperature for 18 h and then at 45 °C for 4 h.

Table 6. Reaction of 3-Acylimidazoles (10) with Alkylbromides



Entry	Compd.	R ¹	R ²	R ³	R ⁴	Reaction time (h)	Yield ^{a)} (%)	Selectivity ^{b)} 11/12
1	10a	H	H	H	C ₆ H ₅ CH ₂	4	93	11a ¹¹ /12a ¹¹ =64/36
2	10b	<i>n</i> -Bu	Cl	H	C ₆ H ₅ CH ₂	2	95	11b ⁹⁾ /12b=89/11
3	10c	H	H	OEt	C ₆ H ₅ CH ₂	2	87	11c ¹²⁾ /12c ¹²⁾ =71/29
4	10d	H	CH ₃	OEt	C ₆ H ₅ CH ₂	2	94	11d ¹³⁾ /12d ¹³⁾ =81/19
5	10e	H	H	OEt	4-I-C ₆ H ₄ CH ₂	2	83	11e/12e=70/30
6	10f	H	CH ₃	OEt	4-I-C ₆ H ₄ CH ₂	2	90	11f/12f=84/16
7	10g	H	H	OEt	CH ₂ =CHCH ₂	1	86	11g/12g=75/25
8	10h	H	CH ₃	OEt	CH ₂ =CHCH ₂	1	95	11h/12h=92/8
9	10i	H	–CH ₂ CH ₂ CH ₂ –	C ₆ H ₅ CH ₂	C ₆ H ₅ CH ₂	4	98	11i/12i=91/9
10	10j	H	H	CH ₃	C ₆ H ₅ CH ₂	4	93	11j/12j ¹⁴⁾ =44/56

^{a)} Total isolated yield of compound (11) and compound (12) is shown. ^{b)} Calculated ratio based on isolated yields of compound (11) and compound (12).

5,6,7,8-tetrahydro-3*H*-cycloheptimidazol-4-one (**3**) and 2-propyl-3*H*-cycloheptimidazol-4-one (**7**) was examined. High regioselectivities were observed under the reaction conditions using aq. NaOH/PTC/toluene. High regioselectivity was observed in the use of a lower alkaline concentration for 2-propyl-5,6,7,8-tetrahydro-3*H*-cycloheptimidazol-4-one (**5**) and a higher alkaline concentration for 2-propyl-3*H*-cycloheptimidazol-4-one (**8**). Application of this alkylation under similar conditions to non-fused 4-acylimidazole did not result in clear regioselectivity in the non-fused ketone compounds. However, relatively high selectivity was observed in the *N*3 alkylation to ester and aldehyde compounds.

Experimental

Melting points were determined on Yamato melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Hitachi 270-30. Proton nuclear magnetic resonance (¹H-NMR) spectra were measured at 400 MHz on a JEOL EX-400 Fourier-transform NMR spectrometer. Chemical shifts are quoted in part per million (ppm) with trimethylsilane as an internal standard. Coupling constants (*J*) are given in Hz. The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; brs, broad singlet; dd, doublet of doublet; m, multiplet. Mass spectra (MS) were taken on a Hitachi M-80B spectrometer. For column chromatography, silica gel (Merck, Kieselgel 60, 70–230 mesh) were used.

General Procedure for 3-[2'-(1-*tert*-Butyl-1*H*-tetrazol-5-yl)biphenyl-4-ylmethyl]-2-propyl-5,6,7,8-tetrahydro-3*H*-cycloheptimidazol-4-one (5**) and 3-[2'-(1-*tert*-Butyl-1*H*-tetrazol-5-yl)biphenyl-4-ylmethyl]-2-propyl-5,6,7,8-tetrahydro-1*H*-cycloheptimidazol-4-one (**6**)** To a mixture of 20% aqueous NaOH (7 ml) and toluene (22 ml), 2-propyl-5,6,7,8-tetrahydro-3*H*-cycloheptimidazol-4-one (1.02 g) and 5-(4'-bromomethyl-biphenyl-2-yl)-1-*tert*-butyl-1*H*-tetrazole (2.20 g) was added tetra-*n*-butylammonium bromide (0.68 g) and the mixture was stirred at room temperature for 2 h. The reaction mixture was treated with excess saturated aqueous ammonium chloride and extracts with toluene (3×50 ml). The combined extracts layers were washed with brine and dried over Na₂SO₄. The solvent was removed under the reduced pressure. The residue was purified by silica gel column chromatography (AcOEt/MeOH=30/1, 10/1), affording pure **5** (2.14 g, 83.5% yield) and pure **6** (0.28 g, 11.1% yield). **5**: Recrystallization from *iso*-propyl ether (IPE), gave colorless powder. mp 87–89 °C. IR (KBr) cm⁻¹: 2914, 1620. ¹H-NMR (CDCl₃) δ: 0.97 (3H, t, *J*=7.2 Hz), 1.55 (9H, s), 1.65–1.80 (2H, m), 1.80–1.95 (4H, m), 2.59 (2H, t, *J*=8.0 Hz), 2.60–2.70 (2H, m), 3.00 (2H, t, *J*=6.0 Hz), 5.56 (2H, s), 6.89 (2H, d, *J*=8.4 Hz), 7.10 (2H, d, *J*=8.4 Hz), 7.39 (1H, dd, *J*=1.6, 7.6 Hz), 7.42–7.54 (2H, m), 7.88 (2H, dd, *J*=1.6, 7.2 Hz). MS *m/z*: 482 (M⁺), 178 (B.P.). **6**: Colorless amorphous substance. IR (KBr) cm⁻¹: 2926, 1653. ¹H-NMR (CDCl₃) δ: 0.96 (3H, t, *J*=7.2 Hz), 1.59 (9H, s), 1.69–1.82 (2H, m), 1.83–1.97 (4H, m), 2.63 (2H, t, *J*=8.0 Hz), 2.71 (2H, t, *J*=6.0 Hz), 2.77 (2H, t, *J*=6.0 Hz), 5.07 (2H, s), 6.84 (2H, d, *J*=8.4 Hz), 7.17 (2H, d, *J*=8.4 Hz), 7.41 (1H, dd, *J*=1.6, 7.6 Hz), 7.45–7.54 (2H, m), 7.90 (2H, dd, *J*=1.6, 7.6 Hz). MS *m/z*: 482 (M⁺), 178 (B.P.), 57.

The following compounds **8**, **9**, **11a–j** and **12a–j** were prepared using a procedure similar to that described **5** and **6** from the corresponding imidazole compounds and alkylhalides.

3-[2'-(1-*tert*-Butyl-1*H*-tetrazol-5-yl)biphenyl-4-ylmethyl]-2-propyl-3*H*-cycloheptimidazol-4-one (**8**): mp 117–119 °C (EtOAc, colorless powder). IR (KBr) cm⁻¹: 2956, 1575. ¹H-NMR (CDCl₃) δ: 1.02 (3H, t, *J*=7.2 Hz), 1.51 (9H, s), 1.84 (2H, m), 2.77 (2H, t, *J*=7.6 Hz), 6.03 (2H, s), 6.89–7.00 (1H, m), 6.95 (1H, d, *J*=8.0 Hz), 7.10 (1H, d, *J*=8.0 Hz), 7.10 (1H, *J*=12.0 Hz), 7.19 (1H, dd, *J*=8.0, 12.0 Hz), 7.38 (1H, dd, *J*=1.6, 7.2 Hz), 7.43–7.54 (2H, m), 7.71 (1H, d, *J*=11.2 Hz), 7.88 (1H, dd, *J*=1.6, 8.8 Hz). MS *m/z*: 478 (M⁺), 178 (B.P.), 57.

3-[2'-(1-*tert*-Butyl-1*H*-tetrazol-5-yl)biphenyl-4-ylmethyl]-2-propyl-1*H*-cycloheptimidazol-4-one (**9**): mp 82–84 °C (EtOAc, colorless powder). IR (KBr) cm⁻¹: 2956, 1579. ¹H-NMR (CDCl₃) δ: 1.02 (3H, t, *J*=7.2 Hz), 1.54 (9H, s), 1.88 (2H, m), 2.87 (2H, t, *J*=8.0 Hz), 5.40 (2H, s), 6.80 (1H, dd, *J*=8.8, 11.6 Hz), 6.90 (2H, d, *J*=8.0 Hz), 7.10 (1H, d, *J*=8.0 Hz), 7.10 (1H, d, *J*=12.0 Hz), 7.31 (1H, d, *J*=12.0 Hz), 7.39 (1H, dd, *J*=1.6, 7.2 Hz), 7.43–7.54 (2H, m), 7.90 (1H, dd, *J*=1.6, 8.8 Hz). MS *m/z*: 478 (M⁺), 178 (B.P.), 57.

3-Benzyl-2-butyl-5-chloro-3*H*-imidazole-4-carbaldehyde (**11b**): mp 93–95 °C (*i*-PrOH, colorless powder, Lit. 94–96 °C). IR (KBr) cm⁻¹: 3009,

1670. ¹H-NMR (CDCl₃) δ: 0.88 (3H, t, *J*=7.2 Hz), 1.33 (2H, m), 1.65 (2H, m), 2.62 (2H, t, *J*=7.6 Hz), 5.55 (2H, s), 7.04 (2H, d, *J*=7.2 Hz), 7.25–7.35 (3H, m), 9.75 (1H, s). MS *m/z*: 276 (M⁺), 234, 91 (B.P.).

1-Benzyl-2-butyl-5-chloro-1*H*-imidazole-4-carbaldehyde (**12b**): Colorless oil. IR (neat) cm⁻¹: 3016, 1685. ¹H-NMR (CDCl₃) δ: 0.86 (3H, t, *J*=7.2 Hz), 1.34 (2H, m), 1.65 (2H, m), 2.62 (2H, t, *J*=7.6 Hz), 5.12 (2H, s), 7.03 (2H, d, *J*=7.2 Hz), 7.26–7.39 (3H, m), 9.92 (1H, s). MS *m/z*: 276 (M⁺), 234, 91 (B.P.).

3-Benzyl-5-methyl-3*H*-imidazole-4-carboxylic Acid Ethyl Ester (**11d**): mp 60–61 °C (IPE, colorless powder). IR (KBr) cm⁻¹: 2974, 1689. ¹H-NMR (CDCl₃) δ: 1.30 (3H, t, *J*=6.8 Hz), 2.51 (3H, s), 4.24 (2H, q, *J*=6.8 Hz), 5.47 (2H, s), 7.13 (2H, d, *J*=7.6 Hz), 7.26–7.39 (3H, m), 7.50 (1H, s). MS *m/z*: 244 (M⁺), 198, 91 (B.P.).

1-Benzyl-5-methyl-1*H*-imidazole-4-carboxylic Acid Ethyl Ester (**12d**): mp 64–65 °C (IPE, colorless powder). IR (KBr) cm⁻¹: 2962, 1692. ¹H-NMR (CDCl₃) δ: 1.40 (3H, t, *J*=6.8 Hz), 2.45 (3H, s), 4.37 (2H, q, *J*=6.8 Hz), 5.09 (2H, s), 7.05 (2H, d, *J*=7.2 Hz), 7.26–7.39 (3H, m), 7.48 (1H, s). MS *m/z*: 244 (M⁺), 198, 91 (B.P.).

3-(4-Iodo-benzyl)-3*H*-imidazole-4-carboxylic Acid Ethyl Ester (**11e**): mp 69–70 °C (IPE, colorless powder). IR (KBr) cm⁻¹: 2974, 1704. ¹H-NMR (CDCl₃) δ: 1.32 (3H, t, *J*=6.8 Hz), 4.26 (2H, q, *J*=6.8 Hz), 5.45 (2H, s), 6.90 (2H, d, *J*=8.4 Hz), 7.62 (1H, s), 7.65 (2H, d, *J*=8.4 Hz), 7.77 (1H, s). MS *m/z*: 356 (M⁺), 217 (B.P.), 90.

1-(4-Iodo-benzyl)-1*H*-imidazole-4-carboxylic Acid Ethyl Ester (**12e**): mp 115–117 °C (IPE, colorless powder). IR (KBr) cm⁻¹: 2962, 1689. ¹H-NMR (CDCl₃) δ: 1.37 (3H, t, *J*=6.8 Hz), 4.35 (2H, q, *J*=6.8 Hz), 5.08 (2H, s), 6.91 (2H, d, *J*=8.4 Hz), 7.54 (1H, s), 7.56 (1H, s), 7.71 (2H, d, *J*=8.4 Hz). MS *m/z*: 356 (M⁺), 217 (B.P.), 90.

3-(4-Iodo-benzyl)-5-methyl-3*H*-imidazole-4-carboxylic Acid Ethyl Ester (**11f**): mp 128–129 °C (EtOAc, colorless powder). IR (KBr) cm⁻¹: 2968, 1695. ¹H-NMR (CDCl₃) δ: 1.31 (3H, t, *J*=6.8 Hz), 2.50 (3H, s), 4.25 (2H, q, *J*=6.8 Hz), 5.40 (2H, s), 6.86 (2H, d, *J*=8.4 Hz), 7.52 (1H, s), 7.65 (2H, d, *J*=8.4 Hz). MS *m/z*: 370 (M⁺), 217 (B.P.), 90.

1-(4-Iodo-benzyl)-5-methyl-1*H*-imidazole-4-carboxylic Acid Ethyl Ester (**12f**): mp 146–148 °C (EtOAc, colorless powder). IR (KBr) cm⁻¹: 2968, 1680. ¹H-NMR (CDCl₃) δ: 1.40 (3H, t, *J*=6.8 Hz), 2.43 (3H, s), 4.37 (2H, q, *J*=6.8 Hz), 5.04 (2H, s), 6.79 (2H, d, *J*=8.4 Hz), 7.48 (1H, s), 7.68 (2H, d, *J*=8.4 Hz). MS *m/z*: 370 (M⁺), 217 (B.P.), 90.

3-Allyl-3*H*-imidazole-4-carboxylic Acid Ethyl Ester (**11g**): Oil. IR (neat) cm⁻¹: 2971, 1685. ¹H-NMR (CDCl₃) δ: 1.36 (3H, t, *J*=6.8 Hz), 4.31 (2H, q, *J*=6.8 Hz), 4.94 (2H, d, *J*=4.4 Hz), 5.08 (1H, d, *J*=16.8 Hz), 5.23 (1H, d, *J*=7.2 Hz), 5.94–6.05 (1H, m), 7.60 (1H, s), 7.75 (1H, s). MS *m/z*: 180 (M⁺), 135, 107 (B.P.).

1-Allyl-1*H*-imidazole-4-carboxylic Acid Ethyl Ester (**12g**): Oil. IR (neat) cm⁻¹: 2972, 1686. ¹H-NMR (CDCl₃) δ: 1.39 (3H, t, *J*=6.8 Hz), 4.36 (2H, q, *J*=6.8 Hz), 4.58 (2H, d, *J*=5.6 Hz), 5.23 (1H, d, *J*=18.0 Hz), 5.34 (1H, d, *J*=10.4 Hz), 5.90–6.03 (1H, m), 7.49 (1H, s), 7.60 (1H, s). MS *m/z*: 180 (M⁺), 135, 107 (B.P.).

3-Allyl-5-methyl-3*H*-imidazole-4-carboxylic Acid Ethyl Ester (**11h**): Oil. IR (neat) cm⁻¹: 2962, 1684. ¹H-NMR (CDCl₃) δ: 1.37 (3H, t, *J*=6.8 Hz), 2.49 (3H, s), 4.32 (2H, q, *J*=6.8 Hz), 4.88 (1H, d, *J*=5.2 Hz), 5.06 (1H, d, *J*=18.8 Hz), 5.20 (1H, d, *J*=11.2 Hz), 5.99 (1H, ddd, *J*=5.2, 11.2, 18.8 Hz), 7.47 (1H, s). MS *m/z*: 194 (M⁺, B.P.), 165, 149.

1-Allyl-5-methyl-1*H*-imidazole-4-carboxylic Acid Ethyl Ester (**12h**): Oil. IR (neat) cm⁻¹: 2969, 1682. ¹H-NMR (CDCl₃) δ: 1.40 (3H, t, *J*=7.2 Hz), 2.50 (3H, s), 4.35 (2H, q, *J*=7.2 Hz), 4.50 (1H, d, *J*=4.8 Hz), 4.99 (1H, d, *J*=17.2 Hz), 5.27 (1H, d, *J*=10.8 Hz), 5.91 (1H, ddd, *J*=4.8, 10.8, 17.2 Hz), 7.42 (1H, s). MS *m/z*: 194 (M⁺), 149 (B.P.), 122.

3-Benzyl-3,5,6,7-tetrahydro-benzimidazol-4-one (**11i**): mp 66–67 °C (IPE, colorless powder). IR (KBr) cm⁻¹: 2932, 1662. ¹H-NMR (CDCl₃) δ: 2.14 (2H, m), 2.52 (2H, t, *J*=6.2 Hz), 2.86 (2H, t, *J*=6.2 Hz), 5.46 (2H, s), 7.26 (2H, m), 7.34 (3H, m), 7.55 (1H, s). MS *m/z*: 226 (M⁺), 91 (B.P.), 65.

1-Benzyl-1,5,6,7-tetrahydro-benzimidazol-4-one (**12i**): Colorless oil. IR (neat) cm⁻¹: 2926, 1662. ¹H-NMR (CDCl₃) δ: 2.14 (2H, m), 2.66 (2H, t, *J*=6.4 Hz), 2.86 (2H, t, *J*=6.4 Hz), 5.10 (2H, s), 7.26 (2H, m), 7.34 (3H, m), 7.57 (1H, s). MS *m/z*: 226 (M⁺), 91 (B.P.), 65.

1-(3-Benzyl-3*H*-imidazol-4-yl)ethanone (**11m**): mp 103–104 °C (IPE, colorless powder). IR (neat) cm⁻¹: 3088, 1656. ¹H-NMR (CDCl₃) δ: 2.45 (3H, s), 5.53 (2H, s), 7.17 (2H, d, *J*=8.0 Hz), 7.31 (3H, m), 7.63 (1H, s), 7.81 (1H, s). MS *m/z*: 200 (M⁺), 158, 91 (B.P.).

1-(1-Benzyl-1*H*-imidazol-4-yl)ethanone (**12m**): mp 62–63 °C (IPE, colorless powder). IR (neat) cm⁻¹: 3100, 1662. ¹H-NMR (CDCl₃) δ: 2.55 (3H, s), 5.14 (2H, s), 7.19 (2H, d, *J*=8.0 Hz), 7.36 (3H, m), 7.54 (1H, s), 7.57

(¹H, s). MS *m/z*: 200 (M⁺), 158, 91 (B.P.).

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