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Efficient Synthesis of Imidazole Derivatives: An Important Synthon for the Preparation of Biologically Active Compounds

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4(5)-Chloro-imidazole-5(4)-carboxaldehyde derivatives are important precursors for the preparation of biologically active compounds. We developed a simple, novel, and efficient method for the synthesis of these compounds. The chemistry described is amenable to large-scale use and is flexible enough to allow the preparation of analogs.

Key Words: Imidazole, *N*-chlorosuccinimide, chloroimidazole, chloroimidazole-carboxaldehyde.

Introduction

4(5)-Chloro-imidazole-5(4)-carboxaldehyde derivatives are important precursors for the preparation of calcium channel modulators[1] and angiotensine receptor antagonists.[2] For this reason, efficient synthesis of these valuable and versatile intermediates is of interest. The existing methodology for the preparation of compounds **6a-d**, however, is problematic.[2−5] Recently, we reported a method for the preparation of compound **6c**.[6] In continuation of our research we expanded our procedure and herein present a reliable and efficient method for the synthesis of compounds **6** that is amenable to large-scale use and analog preparation.

Results and Discussion

There are several methods for the preparation of compounds **6a-d**. Watson[5] reported a 5-step method for the preparation of compounds **6** (Scheme 1).

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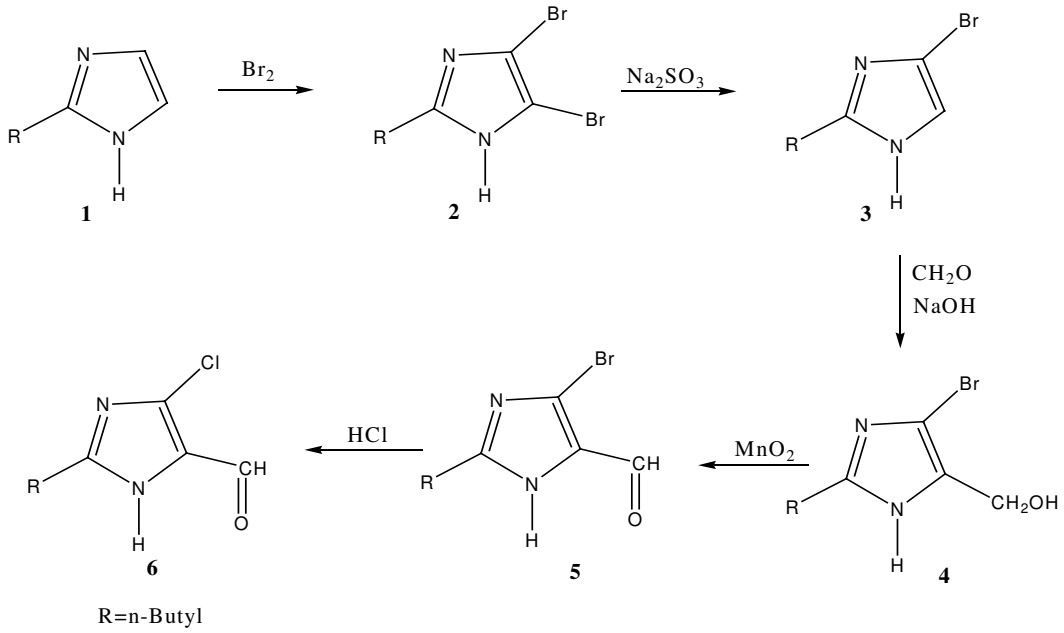
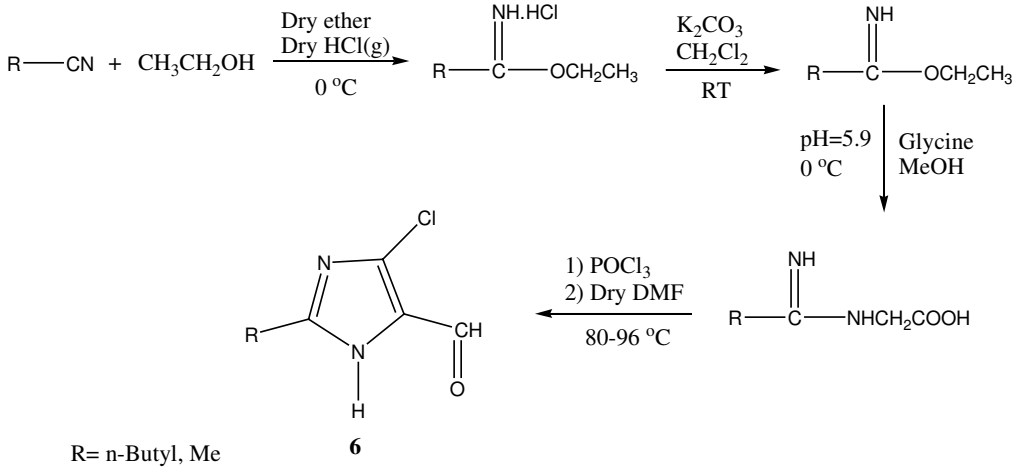


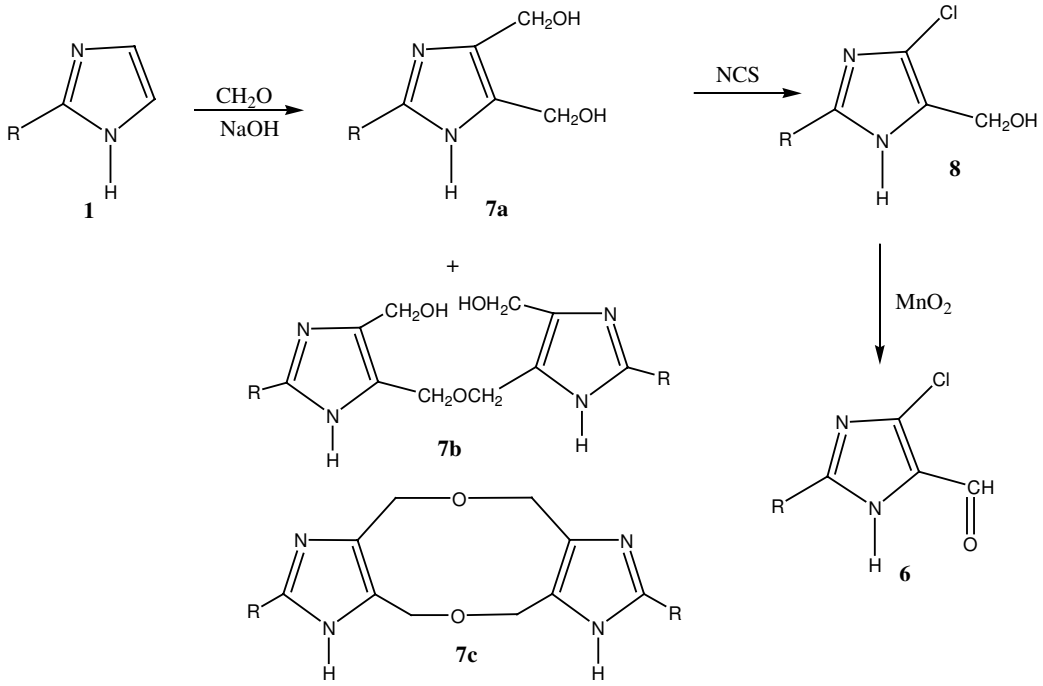
Scheme 1. Synthesis of imidazole derivatives by Watson's method.

The overall yields of the desired compounds are low. In addition, preparation of compound **6a** under the reported conditions is not feasible. Griffiths et al.[2] reported a method for the preparation of 2-butyl-4-chloro-5-formyl- imidazole starting from the corresponding imidate.



Scheme 2. Synthesis of imidazole derivatives according to Griffiths et al.[2]

Preparation of compounds **6b** and **6c** under the reported condition gave low overall yield.[1] In addition, using this method the preparation of compound **6a** was not feasible. Previously, we reported the preparation of compound **6b** using the latter method.[1] Another method[3,4] for the preparation of compounds **6** was reported by Muria et al.[3] and is shown in Scheme 3.



Scheme 3. Synthesis of imidazole derivatives by Muria's method.

2-Alkylimidazole was reacted with formaldehyde and sodium hydroxide solution at 85-95 °C to give compound **7a**. Under the latter conditions, in addition to compound **7a** compounds **7b** and **7c** were also formed. Subsequent reaction of compound **7** with NCS and then MnO_2 gave compounds **6** in low overall yields. In addition, preparation of compound **6a** under the above conditions was not possible.

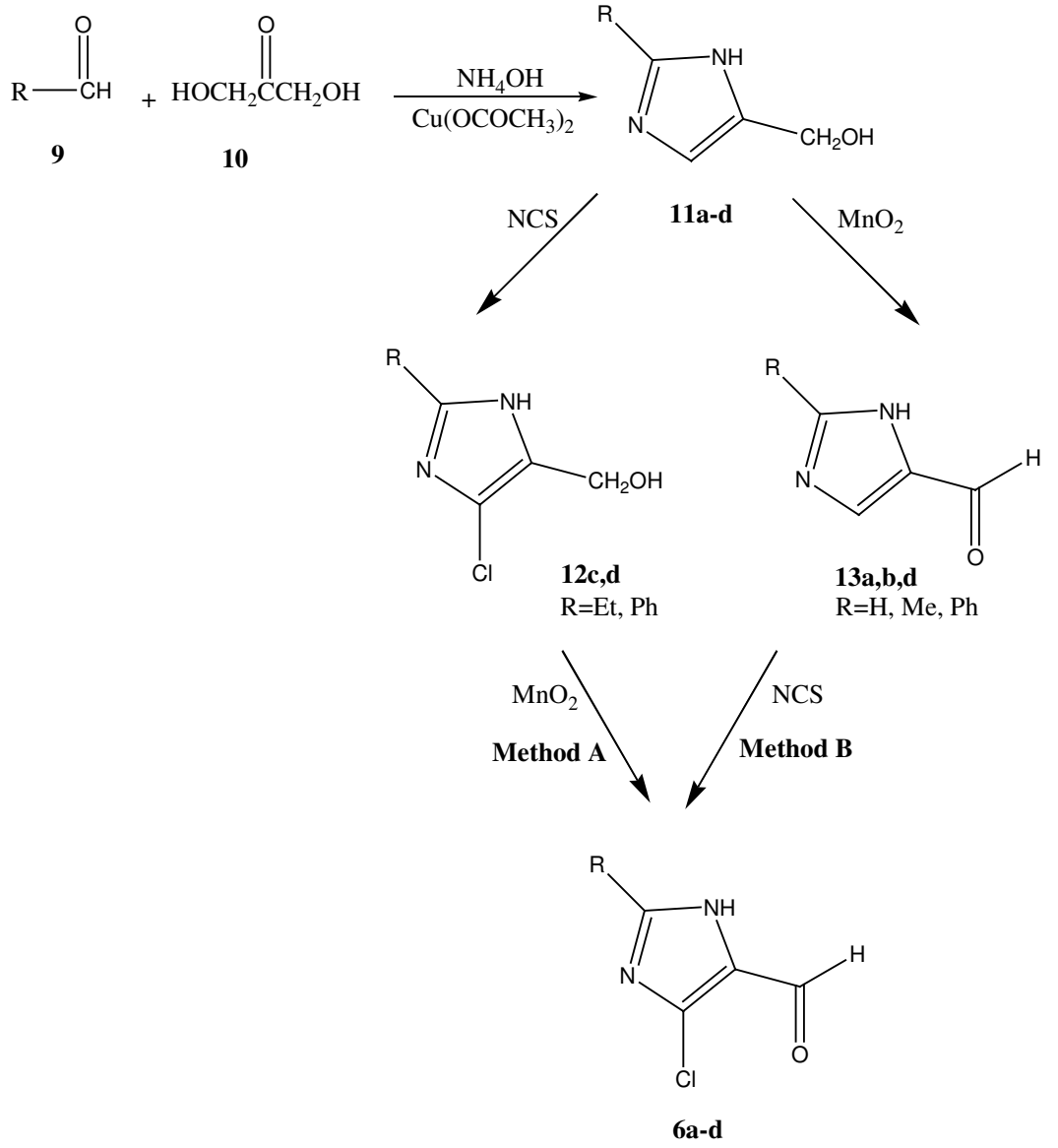
Here we report a new method for the preparation of imidazoles **6a**, **6b**, and **6d** as depicted in Scheme 4. (**6c** was reported previously [6], method A in Scheme 4)

The treatment of the inexpensive and commercially available aldehyde with dihydroxyacetone, ammonia, and copper acetate monohydrate provide directly the alcohols **11**.[7]

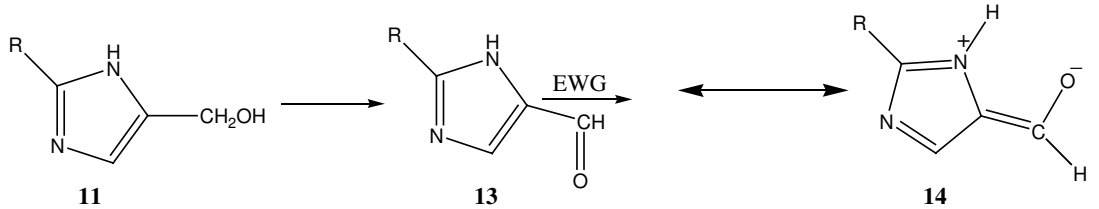
For the preparation of compounds **6a-d**, 2 methods were designed. In method A, 2-ethyl-4(5)-hydroxymethylimidazole (**11c**)[6] and 2-phenyl-4(5)-hydroxymethylimidazole (**11d**) were chlorinated with NCS and the desired 2-ethyl-4(5)-chloro-5(4)-hydroxymethylimidazole (**12c**)[6] and 2-phenyl-4(5)-chloro-5(4)-hydroxylmethyl imidazole (**12d**) were prepared. However, compounds **11a** and **11b** (R= H, Me respectively) could not be chlorinated under similar experimental conditions. A possible explanation for this phenomenon is that the ethyl group causes hindrance for N-chlorination, which resulted in the reduction of the rate of N-chlorination and the desired compound was formed.[8] However, when R=H or Me, N-chlorination was fast, which resulted in the decomposition of the intermediate. Oxidation of compounds **12c** and **12d** with activated manganese(IV) oxide afforded the desired 2-ethyl-4(5)-chloroimidazole-5(4)-carboxaldehyde (**6c**)[6] and 2-phenyl-4(5)-chloroimidazole-5(4)-carboxaldehyde (**6d**).

For the preparation of compounds **6a-b**, method B was developed. For the development of this method, the following reason was considered. When R is a small group such as R= H or R= Me, N-chlorination was fast because of low hindrance in the adjacent nitrogen. In order to reduce the rate of N-chlorination we speculated that oxidation of hydroxymethyl in compound **11** to formyl group (compound

14) caused the reduction of the activity of nitrogen through the electron withdrawing effect and resonance of formyl group, as shown in Scheme 5.



Scheme 4. Synthesis of imidazole derivatives.



Scheme 5. Resonance effect of formyl group.

Oxidation of compounds **11a-b** with activated MnO_2 gave the corresponding aldehydes **13a-b**. Chlorination of the latter compounds with NCS gave the desired compounds **6a-b** in high yield and excellent

purity. Compound **6d** was prepared by both methods A and B and the overall yield of method B was better.

Experimental

Reagents and solvents were obtained from Merck (Darmstadt, Germany). Melting points were determined using a Thomas-Hoover capillary apparatus and were uncorrected. ^{1}H-NMR spectra were recorded on a Bruker FT-500 spectrometer. TMS was used as an internal standard. Infrared spectra were acquired on a Nicollet 550-FT spectrometer. Elemental analyses were carried out with a Perkin-Elmer model 240-C apparatus. The results of elemental analysis (C, H, and N) were within 0.4% of the calculated amounts.

Chemistry. Imidazoles **6a-d** were synthesized according to Scheme 3. Imidazole **11a** was synthesized according to the modified and improved literature procedure.[7] Compounds **11b-11d** were prepared similarly.

4 (5)-Hydroxymethylimidazole (11a)

To a stirred solution of copper acetate(II) monohydrate (131.77 g, 0.66 mol) and concentrated formalin (37%, 150 mL) in concentrated ammonia (25%, 1 L), a solution of dihydroxyacetone (30 g, 0.33 mol) in water (20 mL) was added dropwise over 15 min and heated with stirring for 5 h. The mixture was cooled in an ice-bath, filtered, and washed with water 3 times. The cake was boiled in acetone, filtered, and dried in an oven to give a green copper complex of imidazole (30 g). A suspension of this complex in water (1 L) was treated with H_2S gas for 3 h. The mixture was filtered and washed with water and decolorized with charcoal to give a pale yellow solution. The solvent was removed under reduced pressure and the oily residue (13 g, 40%) was crystallized from acetonitrile to give the title compound as white crystals; mp 87-88 °C; IR (KBr): ν 3100 cm^{-1} (OH); ^{1}H-NMR (DMSO-d_6): δ= 4.43 (s, 2H, CH_2OH), 6.90 (s, 1H, H_4 or H_5- imidazole), 7.57 (s, 1H, H_2-imidazole). Anal. Calcd. for $C_4H_6N_2O$: C, 48.97; H, 6.16; N, 28.56. Found: C, 48.73; H, 6.38; N, 28.33.

2-Methyl-4 (5)-hydroxymethylimidazole (11b)

Using a procedure similar to that for **11a,** acetaldehyde provided **11b** in 40% yield; mp 101-102 °C (ethyl acetate); IR (KBr): ν 3100 cm^{-1} (OH); ^{1}H-NMR (DMSO-d_6): δ= 2.23 (s, 3H, CH_3-imidazole), 4.32 (s, 2H, CH_2OH), 6.71 (s, 1H, H_4 or H_5- imidazole). Anal. Calcd. for $C_5H_8N_2O$: C, 53.36; H, 7.19; N, 24.98. Found: C, 53.02; H, 7.34; N, 24.72.

2-Phenyl-4(5)-hydroxymethylimidazole (11d)

Using a procedure similar to that for **11a,** benzaldehyde provided **11d** in 40% yield; mp 145-147 °C (acetone); IR (KBr): ν 3326 (OH), 3226 (NH), 1624 cm^{-1} (phenyl); ^{1}H-NMR (DMSO-d_6): δ= 4.59 (s, 2H, CH_2OH), 6.96 (s, 1H, H_4 or H_5-imidazole), 7.21-7.65 (m, 3H, phenyl), 7.75-8.11 (m, 2H, phenyl). Anal. Calcd. for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.75; H, 5.82; N, 16.31.

2-Pheny-4(5)-chloro-5(4)-hydroxymethylimidazole (12d)

A mixture of compound **11d** (1 g, 5.74 mmol) and N-chlorosuccinimide (0.76 g, 7.4 mmol) in 2-methoxyethanol (10 mL) and dioxane (15 mL) was stirred at 50 °C for 10 h. Ether (12 mL) was added to the reaction and the precipitate was filtered and crystallized from ethanol to give 0.65 g (54%) of **12d**; mp 191-194 °C (acetone);

IR (KBr): ν 3431 (OH), 3230 (NH), 1624 cm^{-1} (phenyl); ^{1}H-NMR (DMSO-d_6): δ= 4.58 (s, 2H, CH_2OH), 7.37 (d, J=8.0 Hz, 2H, phenyl), 7.95 (m, 3H, phenyl). Anal. Calcd. for $C_{10}H_9ClN_2O$: C, 59.97; H, 4.35; N, 12.72. Found: C, 59.85; H, 4.21; N, 12.69.

Imidazole-4(5)-carboxaldehyde (13a).

A suspension of **11a** (7 g, 0.071 mol) and activated MnO_2 (31 g, 0.35 mol) in acetonitrile (100 mL) was heated at reflux for 24 h. The hot mixture was filtered and washed with warm acetonitrile. The solvent was removed under reduced pressure. The residue was crystallized from CH_2Cl_2 to give the title compound (4.6 g, 70%) as white crystals: mp 146-147 °C; IR (KBr): ν 1665 cm^{-1} (CO); ^{1}H-NMR (DMSO-d_6): δ=7.91 (s, 1H, H_4 or H_5- imidazole), 7.97 (s, 1H, H_2-imidazole), 9.80 (s, 1H, CHO), 10.95 (s, 1H, NH). Anal. Calcd. for $C_4H_4N_2O$: C, 50.00; H, 4.20; N, 29.25. Found: C, 50.28; H, 4.31; N, 29.09.

2-Methyl-imidazole-4(5)-carboxaldehyde (13b).

Using a procedure similar to that for **13a,** compound **11b** provided **13b** in 61% yield; mp 128-131 °C (dichloromethane); IR (KBr): ν 1665 cm^{-1} (CO); ^{1}H-NMR (DMSO-d_6): δ = 2.3 (s, 3H, CH_3-imidazole), 7.58 (s, 1H, H_4 or H_5-imidazole), 9.56 (s, 1H, CHO). Anal. Calcd. for $C_5H_6N_2O$: C, 54.54; H, 5.49, N, 25.44. Found: C, 54.67; H, 5.63; N, 25.65.

5(4)-Chloroimidazole-4(5)-carboxaldehyde (6a).

A solution of **13a** (2.04 g, 0.02 mol) and N-chlorosuccinimide (2.67 g, 0.02 mol) in methanol was heated at reflux in the dark for 24 h. The solvent was removed under reduced pressure and the residue was dissolved in water (20 mL) and filtered. To the filtrate brine (10 mL) was added and extracted with diethyl ether (5 × 100 mL). The organic layer was washed with water (5 mL), brine (5 mL), dried (Na_2SO_4), and evaporated under reduced pressure to give a yellow solid. This was triturated twice with petroleum ether to give the title compound as a white solid (1.9 g, 69%); mp 199-201 °C; IR (KBr): ν 1675 cm^{-1}(CO); ^{1}H-NMR ($CDCl_3$+DMSO-d_6): δ=7.98 (s, 1H, H_2-imidazole), 9.75 (s, 1H, CHO), 12.99 (bs, 1H, NH); ^{13}C-NMR (DMSO-d_6): δ = 185.98 (C=O), 142.53 (C_2, imidazole), 139.59 (C_5, imidazole), 126.68 (C_4, imidazole). Anal. Calcd. for $C_4H_3ClN_2O$: C, 36.81; H, 2.31; N, 21.46. Found: C, 36.74; H, 2.19; N, 21.29.

2-Methyl-5(4)-chloroimidazole-4(5)-carboxaldehyde (6b).

Using a procedure similar to that for **6a,** compound **13b** provided **6b** in 50% yield; mp 149-151 °C; IR (KBr): ν 1675 cm^{-1} (CO); ^{1}H-NMR (DMSO-d_6): δ= 2.32 (s, 3H, CH_3-imidazole), 9.57 (s, 1H, CHO), 13.31 (bs, 1H, NH). ^{13}C-NMR (DMSO-d_6): δ= 177.76 (C=O), 150.78 (C_2, imidazole), 143.55 (C_5, imidazole), 126.61 (C_4, imidazole), 14.87 (CH_3). Anal. Calcd. for $C_5H_5ClN_2O$: C, 41.54; H, 3.49; N, 19.38. Found: C, 41.61; H; 3.64; N, 19.50.

2-Phenyl-5(4)-chloroimidazole-4(5)-carboxaldehyde (6d).

Method A:

A suspension of **12d** (0.5 g, 2.39 mmol) and manganese dioxide (2.5 g, 28.75 mmol) in acetonitrile (5 mL) was heated at reflux for 4 h. The hot mixture was filtered and washed with warm $CHCl_3$. The solvent

was removed under reduced pressure. The residue was purified by column chromatography (silica gel, dichloromethane-ethyl acetate: 10:1) to give **6d** (0.3 g, 60%) as white crystals: mp 172-174 °C; IR (KBr): ν 2126 (NH), 1644 (CO). ^{1}H-NMR ($CDCl_3$): δ=7.55 (m, 3H, phenyl), 8.11 (m, 2H, phenyl), 9.81 (s, 1H, CHO), 11.52 (bs, 1H, NH). ^{13}C-NMR ($CDCl_3$): δ=178.31 (CO), 151.07 (C_2, imidazole), 143.49 (C_5, imidazole), 131.59 (C_1, phenyl), 129.56 (C_3, C_5, phenyl), 127.97 (C_4, phenyl), 127.28 (C_4, imidazole), 127.12 (C_2, C_6, phenyl). Anal. Calcd. for $C_{10}H_7ClN_2O$: C, 57.84; H, 3.88; N, 13.49. Found: C, 57.97; H, 3.95; N, 13.52.

Method B:

Compound **13d** (0.5 g, 2.90 mmol) and N-chlorosuccinimide (0.387 g, 2.90 mmol) were stirred in a mixture of 2-methoxyethanol (5 mL) and dioxane (7 mL) at 65 °C for 24 h. Water (10 mL) was added to the reaction mixture, and extracted with chloroform (3 × 15 mL). The organic layer was washed with water (5 mL), dried (Na_2SO_4), and evaporated under reduced pressure to give a yellow solid. The residue was purified by column chromatography (silica gel, dichloromethane-ethyl acetate: 10:1) to give the title compound (0.372 g, 62%) as white crystals: mp 172-174 ° C.

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