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Synthesis of some substituted imidazole derivatives

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ABSTRACT

Imidazoles are versatile nitrogen heterocyclic compounds displaying a wide-variety of biological and pharmacological activities like anti-inflammatory, hypnotics, sedatives, tranquilizers, antidepressant and anti-parinsonian in animals as well as in human system. The chemistry of imidazoles has been of great interest to medicinal chemists. We are reporting here organic synthesis of some derivatives of imidazoles to evaluating their biological activities.

KEYWORDS

Synthesis;
Imidazoles derivatives;
PDC.

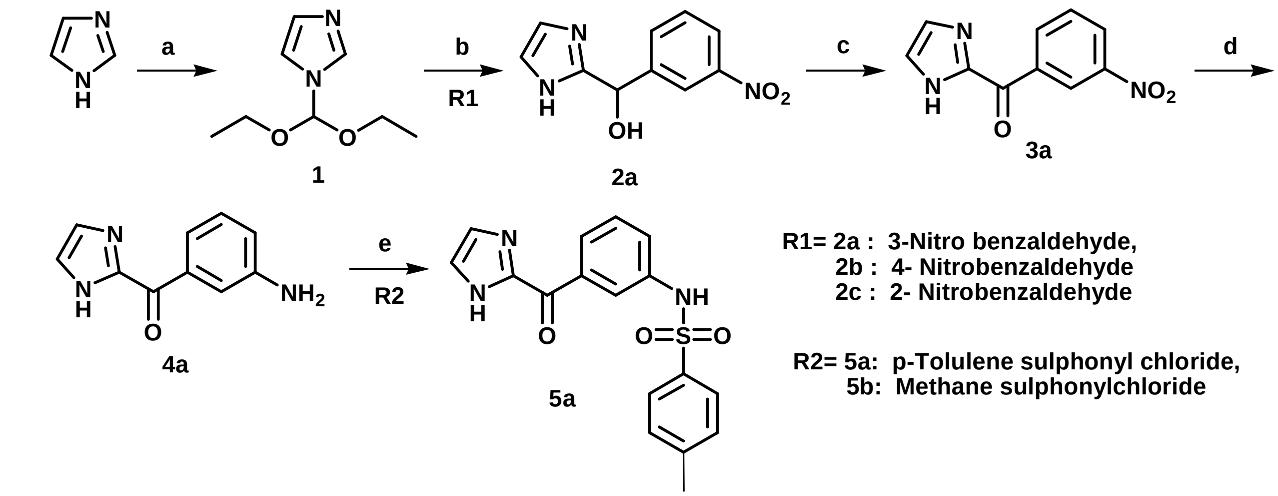
INTRODUCTION

The synthesis of new evaluation heterocyclic compounds are common scaffolds in many drugs and have the attracted the attention of synthetic chemist for over a centaury. We have developed a new synthetic approach for imidazole derivatives. The preparation of saturated and unsaturated compound present a very different picture for it's involve ring synthesis more often than not, of course when first considering a suitable route to a desired target compound. It is always important to give thought to the possibility of utilizing a commercially available compound which contains the heterocyclic nucleus. We have synthesized the imidazole derivative by the protection of imidazole with DEM and lithiation to obtained target scaffold; we have done several acid amine and sulfonamide coupling. Transition-metal mediated cross-coupling reaction have revolutionized organic synthesis many highly efficient and mild protocol for bond construction have emerged by the mastery of such reaction, perhaps the most utilized carbon-carbon bond formation cross-coupling reaction are those that use boron and tin derivative because of their tolerance of a broad range of functional group.

An easily introduced and removed protecting group of imidazole nitrogen more commonly, N-protecting imidazoles are lithiated at C-2 by treatment with n-butyllithium and the corresponding anion is added to electrophillic reagents. For the most part, however, deprotection of imidazole nitrogen involves acidic, basic or reductive conditions and problems are often encountered in either lithiation or addition step. For examples, while N-benzylimidazoles can be readily prepared and the benzyl group removed the lithiation step has been reported to give benzyl deprotonation as well as deprotonation at C-2. N—Alkoxymethyl group direct lithiation to C-2 but their removal requires strong acid reflux and the yields of isolated products are modest to nil. The N-tosyl group is easily introduced and removed, but the nucleophilicity of the C-2 anion is low, we required an N-protecting group which could be easily inserted and if necessary be removed under neutral conditions. The diethoxymethyl function in orthoamide meet, these requirements since it is readily hydrolyzed under neutral or basic condition in few minutes.

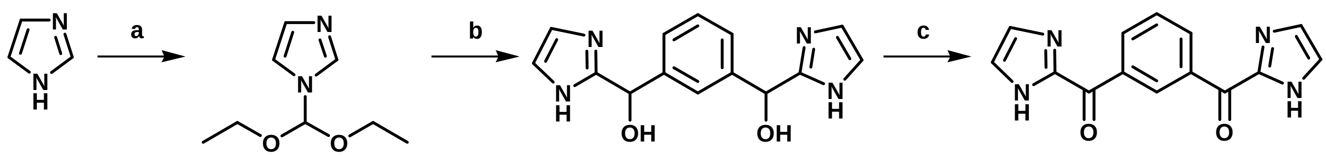
RESULTS AND DISCUSSION

The protected imidazoles are prepared by heating a mixture of imidazole with excess of triethyl orthoformate in presence of an acid catalyst with continuous removal of alcohol produced. The lithiation reactions are carried out in absolute dry THF at -78 ^{0}C, depending upon the solubility of anion, after 1h the electrophilic agent is introduced and the reactions are allowed to come to room temperature overnight. During the reaction we have observed the diethyl acetal group



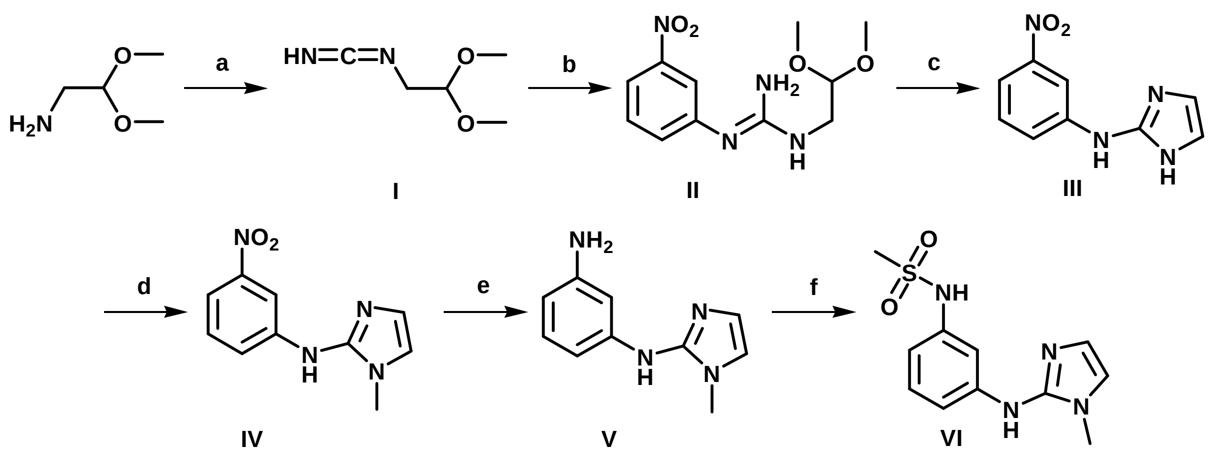
Reagent and conditions: (a) Triethyl orthoformate, PTSA, 135^{0}C, 12h; (b) n-Buli, R_1, THF, -78^{0}C to RT 4h; (c) Pyridinium dichromate, DCM, RT, 4h; (d) Ammonium chloride, Fe powder, MeOH:H_2O, RT, 12h; (d) Triethyl amine, R_2, DCM:THF, RT, 12h.

Scheme 1



Reagent and conditions: (a) Triethyl orthoformate, PTSA, 135^{0}C, 12h; (b) n-Buli, THF, -78^{0}C- RT, 4h; (c) Pyridinium dichromate, DCM, RT, 4h;

Scheme 2



Reagent and conditions: (a) Cyanogen bromide, Ether, 0-35^{0}C,12h; (b) 3-nitroaniline, Methane sulphonic acid, R_1, Ethanol, 78^{0}C,12h; (c) HCl, 5h (d) K_2CO_3, DMF, MeI, RT, 4h; (e) NH_4Cl solution, Fe, THF, Ethanol RT; (f) Methanesulphonyl chloride, Triethyl amine, DCM, 0^{0}C to RT.

Scheme 3

was deprotected. The oxidation we have done by pyridinium dichromate in dichloromethane at room temperature, reduction was done by the saturated ammonium chloride and Fe powder in THF, Ethanol at room temperature for over night and to filtered the reaction mixture and extracted with ethyl acetate. The final amine and sulfonyl chloride coupling was done in dichlomethane and triethyl amine at 0^0C to room temperature for 2-4h.

To 2, 2-Dimethoxy-ethylamine diethyl ether and pentane which was derived from cyanogens bromide to afford a carbodiimide treated with nitro aniline to guanidine, libration of aldehyde with aqueous hydrochloric acid and then treatment with base afforded the desired imidazole in good yield, followed by sulfonamide coupling.

EXPERIMENTAL SECTION

General

Chemicals were commercially available and solvent were anhydrous and dried freshly distilled THF and Ether. All the reactions were carried out under nitrogen atmosphere. Proton NMR spectra were measured on Brukar 400 MHz in the solvent specified. Chemical shift are reported in δ downfield from TMS as an internal standard and coupling constants are reported in Hzs. Mass spectra were recorded in Agilent.

Scheme 1

Preparation of 1-Diethoxymethyl-1H-imidazole (1): To a solution of imidazole (15.0 g, 220 mmol) in triethyl orthoformate (150.0 ml) as solvent was added p-toluenesulfonic acid (1g). The resulting reaction mixture was heated at 130-140^{0}C for 12 hrs in dean stark apparatus until no more removal of ethanol in the reaction. Triethylorthoformate was removed by under reduced pressure and triethyl amine (1.4 ml) were directly loaded on column with silica gel (100-200 Mesh) eluted with 1-4% methanol in dichloromethane to get desired compound **(1)** (31.5g, 84%) as colorless viscous oil.

^{1}H-NMR (400 MHz, $CDCl_3$-d_1): δ 1.24 (t, 6H), 3.61 (q, 4H), 6.08 (s, 1H), 7.12 (m, 2H), 7.74 (m, 1H).

M/Z (M+1)$^+$ 171.125.

Preparation of (1H-Imidazol-2-yl)-(3-nitro-phenyl)-methanol (2a): To a solution of 1-di-ethoxymethyl-1H-imidazole **(1)** (5.0 g, 29.4 mmol) in freshly distilled THF (50.0 ml). Resulting reaction mixture was cooled to -78^{0}C, followed by drop-wise addition of n-butyllithium (3.5M in hexane, 10.5ml, 36.7 mmol) over 35 min. Reaction mixture was stirred additional 1h at same temperature. Then a solution of 3-Nitro-benzaldehyde (4.88 g, 32.34 mmol) in THF (50.0 ml) was added. The resulting reaction mixture was stirred for 12 hr at room temperature. After completion the reaction (as per TLC monitoring) reaction mixture was cooled to 0^0C and quenched by saturated ammonium chloride; added ethyl acetate (100 mL). Separated the organic layer and washed with water (50 ml x 3 times) and brine solution respectively. The combined organics was dried over anhydrous sodium sulphate and concentrated under reduced pressure. Crude was purified over silica gel (100-200 Mesh) column elution with 2-5% methanol-dichloromethane get desired product **(2a)** (4.25g, 66.4%).

^{1}H-NMR (400 MHz, DMSO-d_6): δ 6.45 (brs, 1H), 6.85 (d, 1H), 6.82 (m, 2H), 7.70 (dd, J= 4.4 Hz, 2H), 8.22(dd, J= 4.4 Hz, 2H) and 12.87 (brs, 1H).

M/Z (M+1)$^+$ 220.08.

Preparation of (1H-Imidazol-2-yl)-(3-nitro-phenyl)-methanone (3a): To a solution of (1H-imidazol-2-yl)-(3-nitro-phenyl)-methanol **(2a)** (2.0 g, 9.13 mmol) in dichloromethane (20.0 ml) and added pyridinium dichromate (5.15g, 13.7 mmol). The resulting reaction mixture was stirred for 4 hr at 30^{0}C. After completion the reaction (as per TLC monitoring), reaction mixture was quenched by water (20.0 ml), added dichloromethane (100 mL). Separated the organic layer and washed with water (50.0 mL x 3 times). The Organics dried over anhydrous sodium sulphate. Concentrated the solvent under reduced pressure. Crude was purified over silica gel (100-200 Mesh) elution with 2-5% methanol- dichloromethane to get desired product **(3a)** (1.45g, 73.2%).

^{1}H-NMR (400 MHz, DMSO-d_6): δ 6.84 (m, 2H), 7.72 (dd, J= 4.4 Hz, 2H), 8.25(dd, J= 4.4 Hz, 2H) and 12.90 (brs, 1H).

M/Z (M+1)$^+$ 218.10.

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Preparation of (3-Amino-phenyl)-(1H-imidazol-2-yl)-methanone (4a): To a solution of 1H-Imidazol-2-yl)-(3-nitro-phenyl)-methanone **(3a)** (2.0 g, 9.21 mmol) in methanol (10.0 ml) and added saturated ammonium chloride solution (40.0 ml) as followed by addition of iron powder (2.57g, 46.0 mmol). The resulting reaction mixture was stirred at 30^{0}C for 12 hr. After completion the reaction (as per TLC monitoring). Reaction mixture was filtered through celite bed, washed with ethyl acetate (100.0 ml) and evaporated the solvent under vaccum. The crude residue was diluted with ethyl acetate (100 mL) added water (100.0 mL) and extracted with ethyl acetate (50.0 mL x 3 times). The combined organics dried over anhydrous sodium sulphate and solvent was removed by distillation under vacuum. Crude was purified over silica gel (100-200 Mesh) column elution with 2-7% methanol in dichloromethane, to get desired compound **(4a)** (1.25g, 72.5%).

^{1}H-NMR (400 MHz, DMSO-d$_6$): δ 6.24 (brs, 2H), 6.88 (m, 2H), 7.77 (dd, J= 4.4 Hz, 2H), 8.28 (dd, J= 4.4 Hz, 2H) and 13.00 (brs, 1H).

M/Z (M+1)$^+$ 188.10.

Preparation of N-[3-(1H-Imidazole-2-carbonyl)-phenyl]-4-methyl-benzenesulfonamide (5a): To a ice cooled solution of 3-Amino-phenyl)-(1H-imidazol-2-yl)-methanone **(4a)** (1.2g, 6.41 mmol) in dichloromethane (20.0 ml) added triethylamine (1.19 ml, 8.65 mmol), then followed by addition of 4-Methyl-benzenesulfonyl chloride (1.35g, 7.05 mmol) at same temperature. The resulting reaction mixture was stirred for 5.0 hr at room temperature. After completion the reaction (as per TLC monitoring), reaction mass diluted with water (100.0 ml) and extracted with dichloromethane (100.0 ml x 3 times). The combined organic layer washed with brine solution. The organics dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude was purified over silica gel (100-200 Mesh) column elution with 2-6% methanol- dichloromethane to get desired product **(5a)** (0.85g (48.1%).

^{1}H-NMR (400 MHz, DMSO-d$_6$): δ 2.32 (s, 3H), 4.02 (brs, 1H), 6.32 (d, J=4.2, 2H), 6.65 (d, J=4.2, 2H), 6.87 (m, 2H), 7.79 (dd, J= 4.4 Hz, 2H), 8.35(dd, J= 4.4 Hz, 2H) and 13.05 (brs, 1H).

M/Z (M+1)$^+$ 342.12 .

Scheme 3

Preparation of 2, 2-Dimethoxy-ethyl-carbodiimide (I): To a ice cold solution of 2, 2-di-methoxy-ethylamine (7.0 g, 7.8 mmol) in diethyl ether and pentane (140.0 ml, 1:1) added cynogen bromide (8.33g, 7.8 mmol) portion wise at 0^{0}C, a white precipitate was formed. The resulting reaction mixture was stirred at room temperature for 16.0 hr. After completion the reaction (as per TLC monitoring), the white precipitate was filtered through sintered funnel and filtrate was evaporated under reduced pressure. The crude was purified over silica gel (100-200 Mesh) column elution with 2-4% methanol- dichloromethane to obtained desired compound **(I)** (2.6g, 31.7%).

^{1}H-NMR (400 MHz, CDCl-d$_1$): δ 1.82(d, 2H), 3.60 (s, 6H), 4.02 (t, J=1.8, 1H) and 5.18 (brs, 1H).

M/Z (M+1)$^+$ 131.12.

Preparation of (1H-Imidazol-2-yl)-(3-nitro-phenyl)-amine (II & III): To a solution of 2,2-Dimethoxy-ethyl-carbodiimide **(I)** (5.0g, 38.6 mmol) in ethanol (45.0 mL), then added 3-nitro aniline (6.39g, 46.32 mmol) followed by addition of methane sulphonic acid (4.0g 42.46 mmol). The resulting reaction mass was refluxed at 85.0^{0}C for 24.0 hr. After completion the reaction (as per TLC monitoring), the reaction mass was basified (pH was adjusted to 8-9) with 25% NaOH and reaction mixture was stirred for 1.0 hr at same temperature and the crude (6.2g) was proceeded for further next step without purification **(II)**. The crude N-(2, 2-Dimethoxy-ethyl)-N'-(3-nitro-phenyl)-guanidine **(II)** (6.2g) was cooled to 10.0^{0}C and acidified (pH was adjusted to 1-2) with 6N HCl and stirred the reaction mixture for 4.0 hr at same temperature, again reaction mass was basified (pH was adjusted to 9-10) with 25% NaOH solution and extracted with 5% methanol in DCM (90.0 ml x 3 times). The combined organic layer was dried over sodium sulphate and evaporated under reduced pressure. The crude was purified over silica gel (100-200 Mesh) elution with 0.5-2% methanol in DCM to get the desired product **(III)** (1.1g, 20.0 %) as off white solid.

^{1}H-NMR (400 MHz, DMSO-d$_6$): δ 6.0(s, 2H), 7.64-7.44(d, 1H, J=80Hz), 7.62-7.61(d, 1H, J=16Hz), 7.72-7.72 (d, 1H, J=8Hz) 8.56-8.55(m, 1H) 9.316 (s, 1H) and 10.96 (s, 1H).

M/Z (M+1)$^+$ 205.1

Preparation of (1-Methyl-1H-imidazol-2-yl)-(3-nitro-phenyl)-amine (IV): To a solution of (1H-Imidazol-2-yl)-(3-nitro-phenyl)-amine **(III)** (0.7g, 3.43 mmol) in DMF (10.0 ml) was added K_2CO_3 (0.520g, 3.77 mmol) and followed by the addition of Methyl Iodide (0.487g, 3.43 mmol) at 10^{0}C. The resulting reaction mass was stirred at room temperature for 4.0 hr. After completion the reaction (as per TLC monitoring) added water (50.0 ml) and extracted with ethyl acetate (50.0 ml x 3 times). Combined the organic layer and washed with water and brine solution respectively. The organic layer was dried over anhydrous sodium sulphate and evaporated under vaccum. The crude residue was purified over silica gel (100-200 Mesh), elution with 0.5-1% methanol in dichloromethane to get the desired product **(IV)** (0.35g, 47.25%) as off solid product.

^{1}H-NMR (400 MHz, DMSO-d$_6$): δ 3.53 (s, 3H) 6.71-6.72 (d, 1H, J=12Hz), 6.90-6.91(d, 1H, J=8Hz) 7.50-7.46 (m, 1H), 7.64-7.62 (m, 1H) 7.81 (m, 1H), 8.47-8.48 (m, 1H) and 8.93 (s, 1H)

M/Z (M+1)$^+$ 219.1

Preparation of N-(1-Methyl-1H-imidazol-2-yl)-benzene-1,3-diamine (V): To a solution of (1-Methyl-1H-imidazol-2-yl)-(3-nitro-phenyl)-amine **(IV)** (0.3g, 1.37 mmol) in methanol (7.0 ml) was added saturated ammonium chloride solution (10.0 ml) and followed by addition of iron powder (0.384g, 6.85 mmol). The resulting reaction mixture was stirred for 12 hr at 30.0^{0}C. After completion the reaction (as per TLC monitoring), the reaction mixture was filtered through celite bed and washed with ethyl acetate. The filtrate was concentrated and crude was diluted with water (50.0 ml) and extracted with ethyl acetate (50.0 ml x 3 times). The combined organic layer dried over anhydrous sodium sulphate and solvent was concentrated under reduced pressure. The crude was purified over silica gel (100-200 mesh) column elution with 2-7% methanol-dichloromethane to get desired product **(V)** (0.2g, 77.4%).

^{1}H-NMR (400 MHz, DMSO-d$_6$): δ 3.43 (s, 3H), 4.00 (brs, 2H), 6.00-6.03 (d, 1H, J=12Hz), 6.29-6.33(d, 1H, J=8Hz), 6.47 (m, 1H),6.64 (m, 1H) 6.77-6.92 (t, J=4.0 Hz, 1H), 6.94 (s, 1H) and 7.02(s, 1H)

M/Z (M+1)$^+$ 189.3

Preparation of N-[3-(1-Methyl-1H-imidazol-2-ylamino)-phenyl]-methanesulfonamide (VI): To a ice cold solution of N-(1-Methyl-1H-imidazol-2-yl)-benzene-1,3-diamine **(V)** (0.2g, 1.06mmol) in dichloromethane (10.0 ml) and added triethylamine (0.19 ml,1.32mmol) followed by addition of methanesulfonyl chloride (0.11g, 1.16mmol). The resulting reaction mass was stirred for 5.0 hr at room temperature. After completion the reaction (as per TLC monitoring), the reaction mixture was diluted with water (50.0 ml) and extracted with dichloromethane (20 mL x 3 times). The combined organics washed with water and brine solution respectively. Organic layer was dried over anhydrous sodium sulphate and solvent was removed under vaccum. Crude was purified over silica gel (100-200 mesh) column elution with 2-6% methanol-dichloromethane to get desired product **(VI)** (0.115g, 47.2%).

^{1}H-NMR (400 MHz, DMSO-d$_6$): δ 2.95 (s, 3H), 3.45 (s, 3H), 4.22 (brs, 1H), 6.10-6.12 (d, 1H, J=12Hz), 6.30-6.34(d, 1H, J=8Hz), 6.49 (m, 1H),6.68 (m, 1H) 6.79-6.94 (t, J=4.0 Hz, 1H), 6.97 (s, 1H) and 7.10 (s, 1H)

M/Z (M+1)$^+$ 267.08

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