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Synthesis of New Ethyl 6-(Benzimidazol-2-Yl)-2-Methyl Nicotinate

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Abstract : *2-Acetylbenzimidazole **1a** react with DMF-DMA affording the corresponding enaminones **2a**. The latter, on treatement with ethyl acetoacetate & ammonium acetate in acetic acid at refluxing temperature yield ethyl 6-(benzimidazol-2-yl)-2-methyl nicotinate**3a.** The above reactions are general and was extended to the N-methy 2- acetyl benzimidazole **1b** to synthesise the compounds **2b,3b**. Alternatively synthesis of compounds **1b,2b,3b** was done by N-methylation of compound **1a,2a,3a** with dimethyl sulphate in acetonitrile containing K_2CO_3 as base and TBAB as phase transfer catalyst at room temperature for 3 hrs.*

Keywords: benzimidazole,enaminones.

Introduction :

Benzimidazole is an integral part of vitamin B12 and an attaractive heterocyclic molecule in the drug design and discovery. Different hetyerocyclic substituted benzimidazoles are biologically important molecules having various pharmacological activities[1,2] and attractive molecules in protein kinase inhibitors[3].

P.K. Dubey et al. reported Alkylation studies on pyrazolyl and isoxazoly benzimidazoles which are synthesized from enaminones[4]. Mohamed R. Shaaban et al. reported the synthesis of benzimidazole derivatives from enaminone[5]. S.M. Agamy et al. reported synthesis of polyfunctionally substituted pyridines from enaminones using active methylene reagents and ammonium acetate in acetic acid as solvent[6]. Wagdy M. Eldehna et al. reported the synthesis and anti tubercular activity of Nicotinic Acid Hydrazides[7]

In this work the synthesiszed new compounds ethyl 6-(benzimidazol-2-yl)-2-methyl nicotinates **3a-b** not reported earlier in literature.

Results and discussion :

2-Acetylbenzimidazole **1a** react with DMF-DMA affording the corresponding enaminones **2a**. The latter, on treatement with ethyl acetoacetate & ammonium acetate in acetic acid at refluxing temperature yield ethyl 6-(benzimidazol-2-yl)-2-methyl nicotinate **3a** The above reactions are general and was extended to the N-methy 2- acetyl benzimidazole **1b** to synthesise the compounds **2b,3b**. Alternatively synthesis of compounds1b,2b,3b was done by N-methylation of compound **1a,2a,3a** with dimethyl sulphate in acetonitrile containing K_2CO_3 as base and TBAB as phase transfer catalyst at room temperature for 3 hrs.

.**(Scheme1)**

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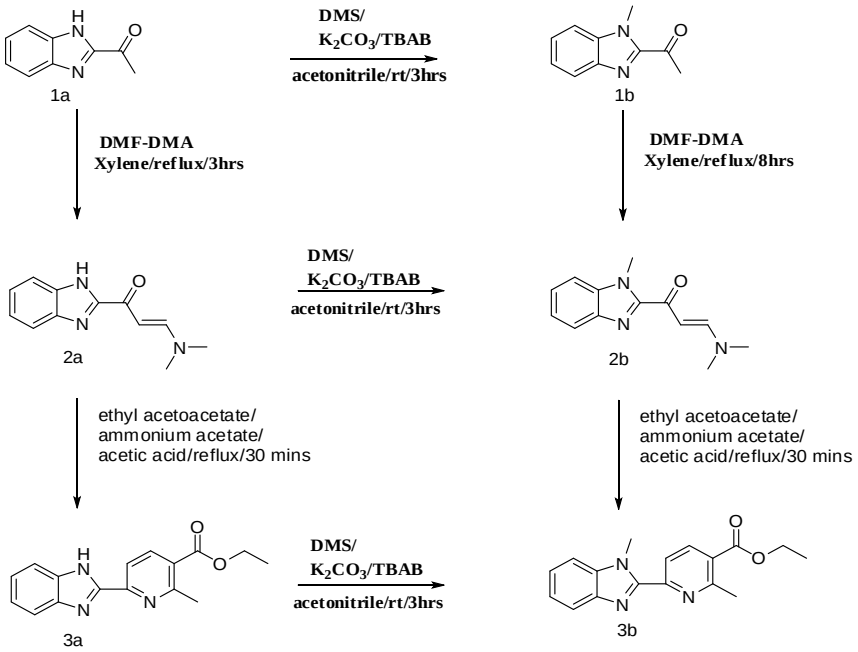
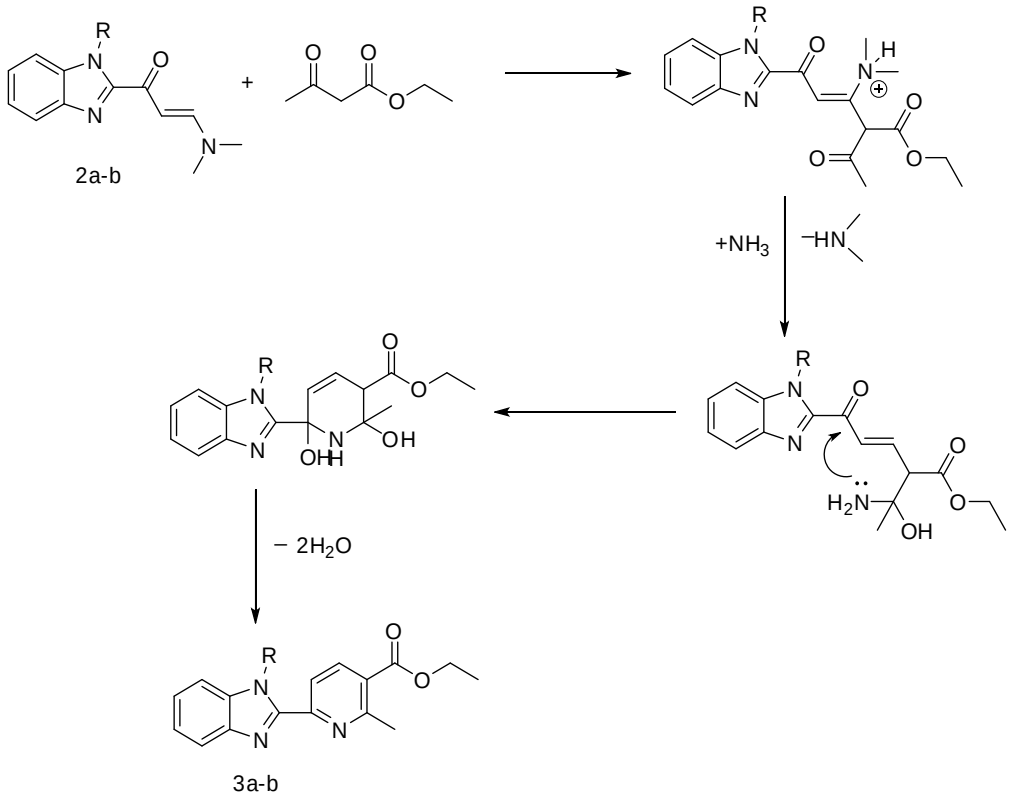
Scheme1:



Formation of ethyl-6-(benzoimidazol-2-yl)-2-methylnicotinates **3(a-b)** was seems to start with Michael addition of ethylacetoacetate to the double bond of enaminones followed by tandem elimination of dimethylamine and condensation with ammonia. Plausible mechanism of the reaction was represented in **(scheme2).**

Scheme-2:



Experimental procedure:

Melting points were determined in open capillaries in sulfuric acid bath. Thin-layer chromatography (TLC) analyses were carried out on glass plates coated with silica gel GF-254 and visualization was achieved using UV lamp. IR spectra were recorded with Perkin – Elmer instrument in KBr pellatization. ^{1}H-NMR were recorded in $CDCl_3$ / DMSO using 400-MHz instrument and Mass spectra were recorded on an Agilent LC-MS instrument giving both M-, M + values in positive and negative modes.

Synthesis of compound **1a-b, 2a-b** was done by as earlier reported procedure from our laboratory[4,8].

General procedure for the preparation of compounds 3a-b:

To solution of suitable compounds 2a-b (23.5mmol) in acetic acid (30ml) added ethyl aceto acetate (27.9 mmol) and ammonium acetate (69.7mmol) at room temperature and heated to refluxing temperature about 3 hrs and after completion of the reaction (monitored by TLC) cool the reaction mass to room temperature and poured the reaction mass to ice cold water and solid separated was filtered and washed with water and dried in hot air oven got pure compounds directly without recrystalization.

3a : Yield=70% ; solid; M.P. = 158^{0}c-160^{0}c; IR(KBr,cm$^-$) 1740, 3384; 1H NMR(DMSO-d_6 , ppm) : 1.34 (t,3H,CH_3), 2.87(S,3H,CH_3), 4.328(q,2H,CH_2), 7.21(m,2H,Ar-H), 7.58(d,1H,Ar-H), 7.71(d,1H,Ar-H), 8.25(d,1H,Ar-H) , 8.34(d,1H,Ar-H); M/Z=282.1(M+1).

3b : yield=65%; solid; M.P.= 70^{0}c-72^{0}C ;IR(KBr,cm$^-$): 3384 ;1H NMR(DMSO-d6,ppm): I.34(t,3H,CH_3) 2.85(S,3H,CH_3), 4.30(S,3H,CH_3), 4.32(q,2H,CH_2), 7.27(m,2H,Ar-H), 7.67(d,1H,Ar-H), 7.73(d,1H,Ar-H), 8.27(d,1H,Ar-H), 8.34(d,1H,Ar-H);M/Z=296.34(M+1).

Alternative procedure for the preparation of compounds 3a-3b:

To a solution of suitable compound 3a-b (17.7mmol) in acetonitrile (30ml) added K_2CO_3 (35.5mmol) and TBAB catalytic amount at room temperature and stirred for 30 mins at room temperature and ofter added dimethyl sulphate(35.5mmol) about three hours and after completion of the reaction (monitored by TLC) poured the reaction mass into ice cold water and solid separated was filtered and dried in hot air oven got pure compound directly without recrystalization .

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