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A Sequential Synthesis of 3-(5-nitro-4 thiocyanatopyrimidin-2-yl)-3H-benzo[d]imidazole-5-carbonitrile

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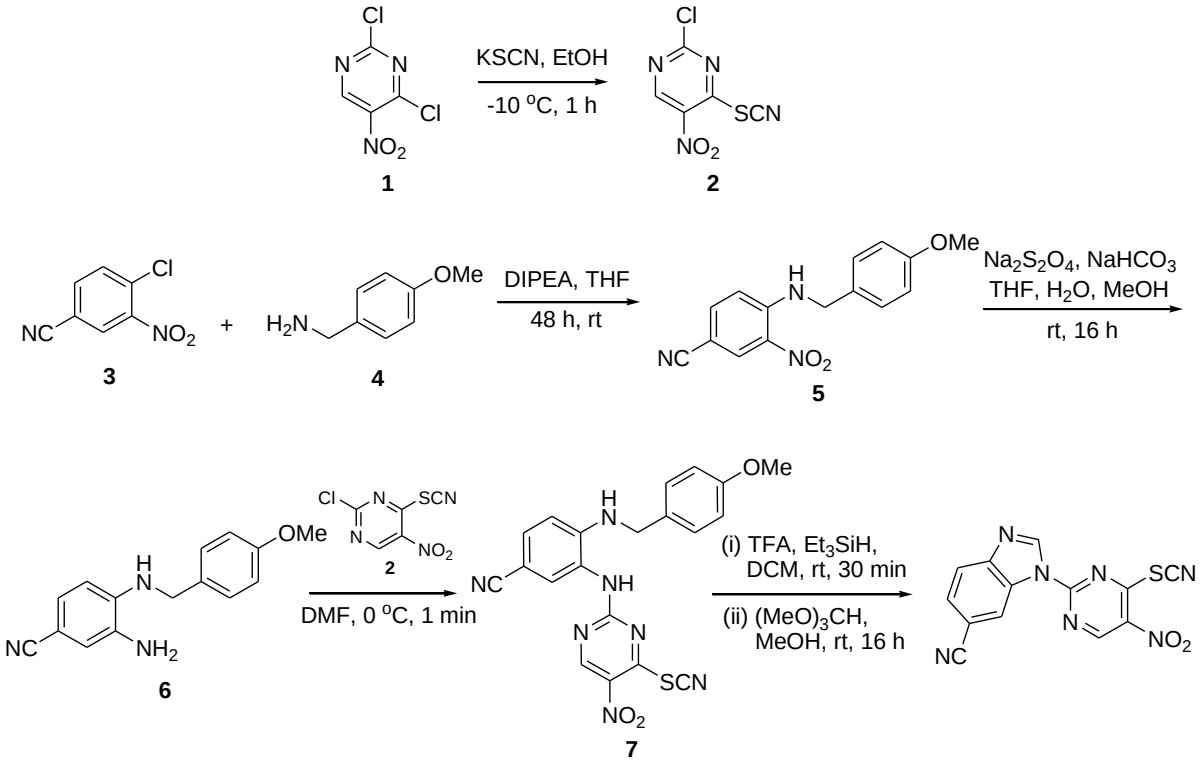
Abstract-The reaction between 2-chloro-5-nitro-4-thiocyanatopyrimidine **(2)** with 4-(4-methoxybenzylamino)-3-aminobenzonitrile **(6)** under DMF at 0 ^{o}C and stirred for 1 min at 0 ^{o}C. The reaction mixture poured into ice-water. Obtained solid was filtered, washed with water and dried to give desired product 4-(4-methoxybenzylamino)-3-(5-nitro-4-thiocyanatopyrimidin-2-ylamino)benzonitrile **(7).***It* was dissolved in DCM and separated the layers. The organic layer was taken in reaction flask. TFA and triethylsilane were added consecutively. The reaction mixture was stirred for 30 min at rt. Reaction mixture was concentrated under high vacuum to get red color residue. Resulting solid was filtered to give desired final product3-(5-nitro-4-thiocyanatopyrimidin-2-yl)-3H-benzo[d]imidazole-5-carbonitrile **(8)** with excellent yields. (**Scheme I**) and Table-1. The structures of the compounds were elucidated by spectral analysis.
Keywords- Imidazole-carbonitrile , TFA, DCM, thiocyanatopyrimidine.

1. INTRODUCTION

Nitrogen containing heterocyclic compounds possessing a wide variety of biological activities. Substituted 1,2,4-triazoles and their derivatives are key skeletons of many biologically active molecules[1-4]and they exhibit wide applications in pesticides, medicines, functional materials, and organ catalysts. These compounds are widely found in bioorganic and medicinal chemistry with applications in drug discovery such as antitumor, anticonvulsant and antiviral applications. [5-7] The imidazoles core structure is found in a variety of cytotoxic natural products, such as the anti mycobacterial, pseudopteroxazole[8,9] and salvianen.[10] The small and simple benzimidazoles nucleus is present in many compounds involved in research aimed at evaluating new products that possess interesting biological activities.[11]

2. EXPERIMENTAL SECTION

Melting points were determined on a Cintex melting point apparatus and are uncorrected. The ^{1}H NMR spectra were recorded on a BRUKER Spectrometer (400 MHz). Chemical shifts were reported in parts per million using tetramethylsilane as an internal standard and were given in δ units. The solvent for NMR spectra was DMSO. Infrared spectra were taken on SHIMADZU-FTIR-8400 Spectrophotometer instrument in the frequency range of 4000-400 cm-1 by KBr powder method. The Mass spectra were recorded by MS-SHIMADZU-QP2010. All reactions were monitored by thin layer chromatography, carried out on 0.2 mm silica gel 60F254 (Merck) plates using UV light for detection. Common reagent grade chemicals are either commercially available and were used without further purification.



Scheme I

3. RESULTS AND DISCUSSION

Synthesis of compounds 2,5,6,7&8

2-chloro-5-nitro-4-thiocyanatopyrimidine (2): 2,4-Dichloro-5-nitropyrimidine was dissolved in ethanol and cooled to -10 °C. Potassium thiocyanate was added and stirred for same temperature for 1 h. Reaction mixture was poured into water and resulting solid was filtered, dried to get product. Solid was triturated with diethyl ether to obtain almost pure product.

4-(4-methoxybenzylamino)-3-nitrobenzonitrile (5): A solution of 4-chloro-3-nitrobenzonitrile in THF was treated with DIEA and 4-methoxybenzylamine, and then stirred at room temperature for 48 h. Reaction mixture was diluted with water, aqueous layer was extracted with EtOAc and combined organic layer was washed with water, brine, dried over anhydrous Na_2SO_4, filtered and concentrated.

4-(4-methoxybenzylamino)-3-aminobenzonitrile (6): A solution of compd-5 in THF was treated with a solution of sodium hydrosulphite and sodium bicarbonate in distilled water. Methanol was immediately added to maintain a homogeneous solution and stirred at room temperature for 16 h. Reaction mixture was diluted with water and extracted with ethyl acetate. Combined organic layer was washed with water, brine, dried over anhydrous Na_2SO_4, filtered and concentrated.

4-(4-methoxybenzylamino)-3-(5-nitro-4-thiocyanatopyrimidin-2-ylamino)benzonitrile (7): Compd-2 was added as a single portion to the solution of compd-6 in dry DMF at 0 °C and stirred for 1 min at 0 °C. The reaction mixture poured into ice-water. Obtained solid was filtered, washed with water and dried for 15 min.

3-(5-nitro-4-thiocyanatopyrimidin-2-yl)-3H-benzo[d]imidazole-5-carbonitrile (8):
Prior to the reaction, the wet compd-**7** was dissolved in DCM and separated the layers. The organic layer was taken in reaction flask. TFA and triethylsilane were added consecutively. The reaction mixture was stirred for 30 min at rt. Reaction mixture was

concentrated under high vacuum to get red color residue. Resulting solid was filtered.

Table-1 Physical and analytical data of Compounds 2,5,6,7 &8 :

S.No	Entry	Physical state	Yield(%)	IR υ (cm^{-1})	^{1}H NMR ($CDCl_3$) δ	*GCMS*: *m/z*$(M+H)^+$
1	2	Yellow solid	68	3431.52 (NH),3034 .09 (C-H aromatic), 1568.32(C=S)	9.41 (s, 1H)	217
2	5	Yellow crystals	78	3381.19 (NH), 3093.19(C-H aromatic), 2222.35 (CN)	9.05 (brs, 1H), 8.52 (s, 1H), 7.76 (d, 1H), 7.32 (d, 2H), 7.05 (d, 1H), 6.86 (d, 2H), 4.62 (d, 2H), 3.76 (s, 3H)	284
3	6	White solid	80	3380 (NH), 2914 (C-H aromatic), 2211 (CN)	7.24 (d, 2H), 6.86 (m, 1H), 6.40 (d, 1H), 6.01 (brs, 1H), 5.12 (brs, 2H), 4.30 (d, 2H), 3.72 (s, 3H)	254
4	7	Orange solid	78	3380 (NH), 2914 (C-H aromatic), 2211 (CN), 1569.12(C=S)	9.18 (s, 1H), 8.52 (brs, 1H), 7.82 (brs, 1H), 7.72 (s, 1H), 7.55 (s, 1H), 7.15 (d, 2H), 6.92 (d, 2H), 6.92 (d, 2H), 6.80 (d, 1H), 5.20 (brs, 2H), 4.42 (s, 2H), 3.82 (s, 3H)	434
5	8	Yellow solid	85	3383 (NH), 3125 (C-H aromatic), 2230 (CN)	10.20 (s, 1H), 9.81 (s, 1H), 9.60 (s, 1H), 8.22 (d, 1H), 8.02 (d, 1H)	324

4. CONCLUSION

We have developed an efficient strategy for the synthesis of 3-(5-nitro-4-thiocyanatopyrimidin-2-yl)-3H-benzo[d]imidazole-5-carbonitrile. This method provides the desired products under operationally simple and convenient conditions with good yields. This approach involves a simple experimental procedure with broad substrate scope and is sustainable to wide range of functionalities.

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