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Efficient one-pot synthesis of multi-substituted triazolopyrimidines by using DBU as basic catalyst via MCR's

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ABSTRACT

One-pot synthesis of various [1, 2, 4]-triazolo [4, 3-a] pyrimidine derivatives from condensation of 3-amino-[1, 2, 4]-triazole, malononitrile and aryl aldehydes using DBU in ethanol under reflux. The targeted molecules are obtained in better yields and take lower reaction times.

Keywords: [1, 2, 4]-Triazolo[4, 3-a] pyrimidine derivatives; DBU; one-pot synthesis; multi component reactions.

INTRODUCTION

Due to their versatile biological activities heterocyclic compounds attract much attention in organic synthesis. Thus development of general methods for synthesis of them is highly valuable. Pyrimidine's are important building blocks in a wide number of biologically active compounds. Interest in pyrimidine containing structures stems from their widespread occurrence in molecules that exhibit significant activity as antibacterial, antifungal, antitumor, antiviral, anti-inflammatory and antihypertensive agents. [1-3]

Currently heterocyclic bearing a [1, 2, 4]-triazole moiety, represent an interesting class of compounds possessing a wide spectrum of therapeutical activities such as anti-inflammatory, antiviral and antimicrobial properties [4-7]. Ribavarin(antiviral), Rizatriptan(antimigrain), Alprazolam (anxiolytic), Vorozole, Letrozole, Anastrozole (antitumoral) are some examples of drugs constituting a structural unit of [1, 2, 4]-triazole moiety [8-9]. Our literature search revealed that although condensation of aromatic aldehydes with 3- amino [1,2,4]triazole and malononitrile took place in the presence of reagents like NaOH[17], Boric acid[16], triethylamine, PTC in water[18] etc., the reactions are not very fast and high yielding.so we introduced DBU(1,8-Diazabicyclo[5.4.0]undec-7-ene) in this protocol as it is sterically hindered amidine base and especially useful where side reactions due to the inherent nucleophilicity of a basic nitrogen are a problem[10-15].In the present paper, one-pot, multi-component protocol for the synthesis of [1,2,4]-triazolo [4,3-a] pyrimidine derivatives was described.

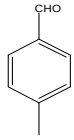
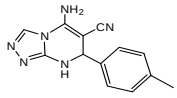
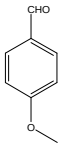
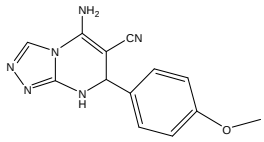
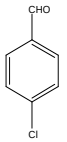
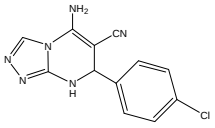
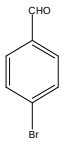
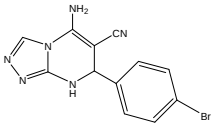
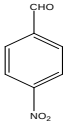
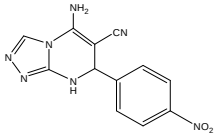
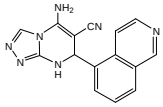
MATERIALS AND METHODS

The chemicals used in this work were obtained from sigma Aldrich used directly without purification. Melting points were determined on a capillary melting point apparatus and are uncorrected. 1HNMR spectral data were recorded on the Bruker-Avance 400-MHz spectrometer in DMSO-d6.The chemical shift values were reported on the δ scale in parts per million (ppm), downfield from tetramethylsilane (TMS) as an internal standard. The purity

determination of the substrates and reaction monitoring were accomplished by TLC on silica-gel plates (from Merck Company). All the products7 (a–f) are known compounds and were characterized by comparison of their 1H NMR spectrum, physical properties, and elemental analyses data with previous synthetic products.

Experimental:
3-amino-1, 2, 4-triazole (1mmol), malononitrile(1mmol) and an aromatic aldehyde (1mmol) in ethanol were placed in a 250ml round bottomed flask. The mixture was stirred for 15 min at room temperature. DBU (1 equivalent) as a baseadded to the above mixture and reflux.The progress of the reaction was monitored by TLC. The reaction mixture was then cooled, filtered and washed with ethanol. The corresponding pure products 7(a-f) were obtained by crystallization from ethanol (Table 1).

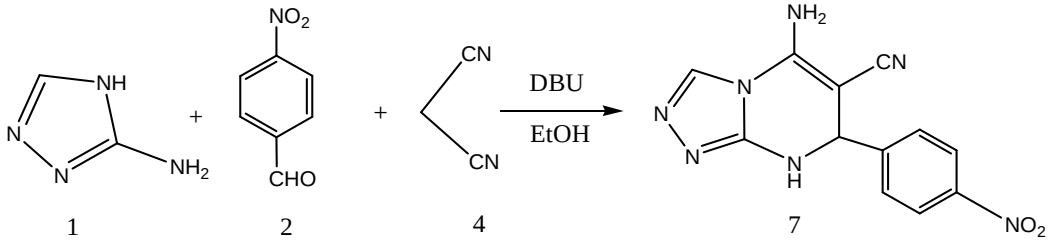
Table 1.DBU catalyzed synthesis of multi-substituted triazolopyrimidines

Entry	Aldehyde	Product
1.		 7a
2.		 7b
3.		 7c
4.		 7d
5.		 7e
6.		 7f

RESULTS AND DISCUSSION

Inspired by the above experiments our programme aimed at developing new selective methodologies for the preparation of heterocyclic compounds, we describe here in efficient methods for the synthesis of new derivatives of trazolopyrimidines .our initial attempts started with the reaction of aromatic aldehyde,3-amino-[1,2,4]-triazole and malononitrile in the presence of DBU as a basic catalyst.In order to evaluate the efficiency of this method the synthesis of multi-substituted triazolopyrimidine'svia reaction ofp-nitro benzaldehyde, 3-amino-[1, 2, 4]-triazole and malononitrile as a model system, was carried out in water using DBU as a catalyst [16].DBU is an organic base(pKa = 12) as + M effect of the adjacent nitrogen stabilizes the protonated species.

Scheme 1: Reaction for the formation of multi-substituted triazolopyrimidines from three components



1 2 4 7

First we investigated the effect of quantity of DBU on the synthesis of triazolo pyrimiines. The reaction was investigated in the presence of 0.1, 0.5, 1.0 and 2.0 equivalents of DBU. In all cases the reaction times were 15min. It was observed that the use of 1 equivalent DBU under reflux yielded the desired product in 92% yield.

In order to assess the effect of the base on the reaction, a range of both organic and inorganic bases were examined.Among the different catalysts tested, DBU and NaOH were the most effective, whereas weaker bases pyridine and piperidine, led to lower yields. In the absence of any catalyst, no reaction is observed (Table 2).

Table 2.Optimization conditions for base

Entry	catalyst	Time	yield
1.	DBU	15min	92%
2.	Piperidine	4-6hrs	60%
3.	Pyridine	4-6hrs	-

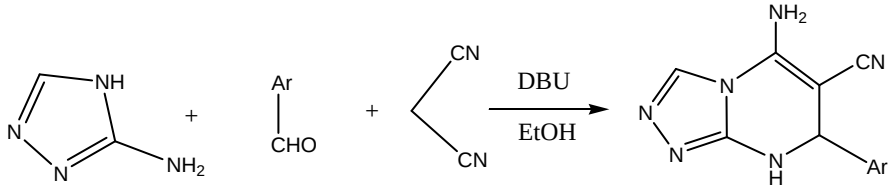
Next the reaction attempted at different temperatures ranging from 25-70^{0}C.it was found that the yield of product significantly increased. The reaction worked best at 70^{0}C.We thought of varying the nature of solvent to increase the product yield, so carried out the reactions in EtOH, H_2O and CH_3CN under reflux. We observed the maximum yield of desired product under reflux at 70^{0}c inEthanol as a solvent within 15min in presence of DBU as a base (Table 3).

Table 3.Optimization conditions for Solvent

entry	Solvent	Time	yield
1.	EtOH	15min	84%
2.	CH_3CN	4-6hrs	60%
3.	H_2O	4-6hrs	-

Based on the optimized reaction conditions established above ,a series of 5-amino-7 aryl-7,8-dihydro-[1,2,4]-triazolo[4,3-a]pyrimidine-6-carbonitriles were prepared by refluxing at 70^0 c by using DBU as a base in EtOH table(4).From the above optimized conditions, successfully synthesized the different triazolopyrimidines by changing different aromatic aldehydes as shown in scheme 2(table 4).

Scheme 2: General reaction



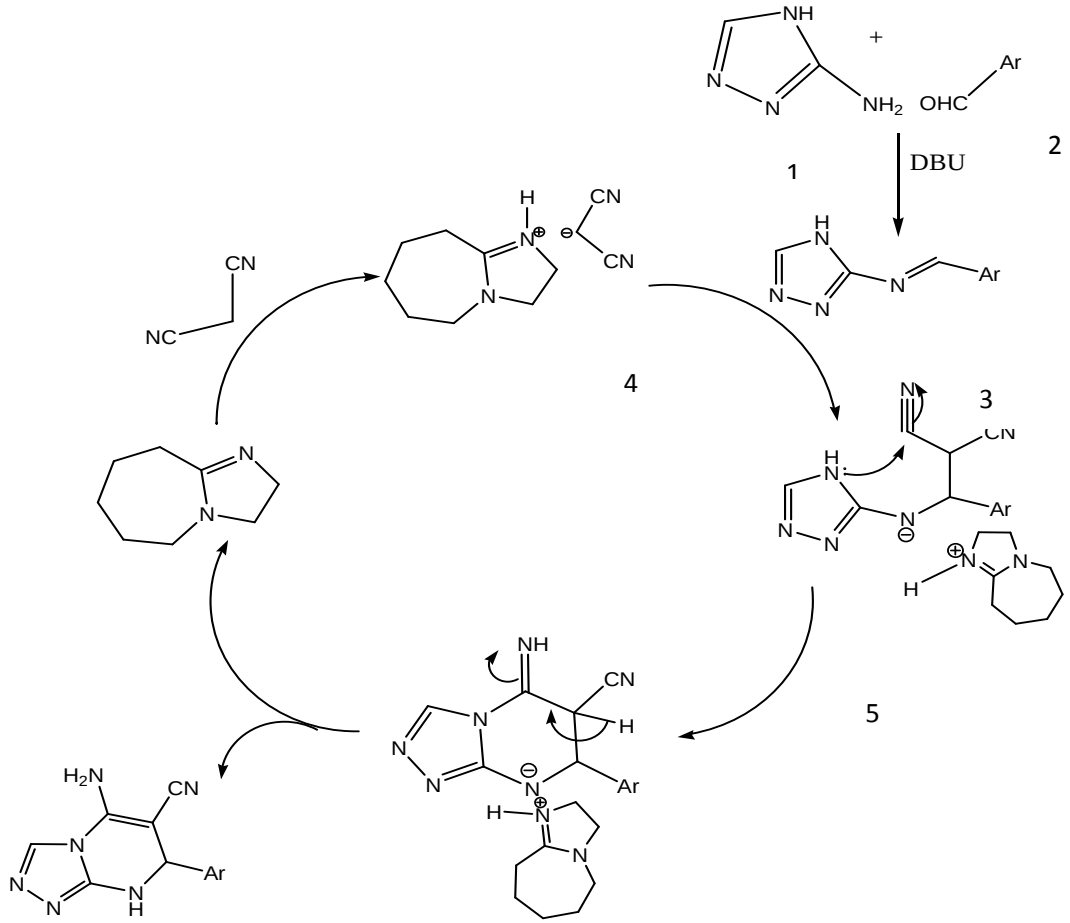
1 2(Ar = a-f) 4 7(Ar = a-f)

Table (4) The synthesis of multi substituted [1, 2, 4]-triazolo [4, 3-a-] pyrimidine's

Entry	Ar	Product	MP	Time	Yield
1	4-Me-C6H4	7a	242−243 °C	0-15min	84%
2	4-MeO-C6H4	7b	218−219 °C	0-15min	90%
3	4-Br-C6H4	7c	262−264 °C	0-15min	90%
4	4-Cl-C6H4	7d	252−256 °C	0-15min	90%
5	4-NO_2-C_6H_4	7e	245−247 °C	0-15min	92%
6	C_9H_9N	7f	241−243 °C	0-15min	82%

Mechanism:
Concerning the reaction mechanism, it is conceivable that the initial step is the condensation between aminotriazole 1 and an aldehyde 2 to afford intermediate 3,and then the subsequent reaction between intermediate 3 and malononitrile 4 takes place to form the intermediate 5.Furthermore ,the intramolecular Michael additionbetween the NH and CN groups of the intermediate molecule 6 resulted in the formation of an intermediate product 6,which was further converted to a final product 7through ionization(scheme 2).Here we believe that higher basicity and stability of DBU-H^+increases the yield of product.

Scheme2: *plausible mechanism for the formation of multi-substituted triazolopyrimidine's.*



Spectra a

Compound-7a:
5-Amino-7-(4-Methylphenyl)-7,8-dihydro-[1,2,4]-triazolo[4,3-a]pyrimidine-6-carbonitrile . White tiny crystals; mp = 242−243 °C. 1H-NMR δ: 2.26 (s, 3H, CH_3), 5.24 (d, 1H, J = 2.4 Hz, CH), 7.19 (s, 2H, NH_2), 7.14−7.15 (dd, 4H, J = 8.4 Hz, p-H_3C-C_6H_4), 7.74 (s, 1H, CH), 8.71 (d, 1H, J = 2.4 Hz, NH). 13C-NMR δ: 20.57, 53.64, 56.02, 118.97, 125.92 (2C), 129.10 (2C), 137.17, 140.19, 146.85, 151.75, 153.86. IR (υ/cm−1): 3248, 3175, 3105, 3043, 2196, 1665, 1625, 1525, 1477, 1443, 1219, 1149.

Compound -7b:
5-Amino-7-(4-methoxyphenyl)-7,8-dihydro-[1,2,4]-triazolo[4,3-a]pyrimidine-6-carbonitrile. White tiny crystals; mp = 218−219 °C. 1H-NMR δ: 3.79 (s, 3H, OCH_3), 5.21 (s, 1H, J = 2.4 Hz, CH), 6.87 (d, 2H, J = 8.4 Hz, p-H_3CO-C_6H_4), 7.28 (d, 2H, J = 8.4 Hz, p-H_3CO-C_6H_4), 7.11 (s, 2H, NH_2), 7.61 (s, 1H, CH), 8.62 (s, 1H, NH). 13C-NMR δ: 53.39, 55.11, 56.18, 113.90 (2C), 118.96, 127.34 (2C), 135.12, 146.81, 153.80, 158.92. IR (υ/cm−1): 3364, 3257, 3127, 3027, 2177, 1678, 1635, 1506, 1474, 1247, 1169, 1019.

Compound-7c:
5-Amino-7-(4-bromolphenyl)-7,8-dihydro-[1,2,4]-triazolo[4,3-a]pyrimidine-6-carbonitrile.
White tiny crystal; mp = 262−264 °C. 1H-NMR δ: 5.31 (d, 1H, J = 2.0 Hz, CH), 7.17 (s, 2H, NH_2), 7.19 (d, 2H, J = 8.4 Hz, p-Br-C_6H_4), 7.69 (d, 2H, J = 8.4 Hz, p-Br-C_6H_4), 7.63 (s, 1H, CH), 8.77 (d, 1H, J = 2.4 Hz, NH). 13C-NMR δ: 53.28, 55.43, 118.80, 121.04, 128.32 (2C), 131.53 (2C), 142.40, 146.98, 151.84, 153.76; IR (υ/cm−1): 3242, 3169, 3125, 2906, 2205, 1649, 1621, 1526, 1475, 1349, 1149, and 1061.

Compound -7d:
5-Amino-7-(4-chlorophenyl)-7,8-dihydro-[1,2,4]-triazolo[4,3-a]pyrimidine-6-carbonitrile.
White crystals; mp = 252−256 °C. 1H-NMR δ: 5.31 (d, 1H, J = 2.4 Hz, CH), 7.19 (s, 2H, NH_2), 7.27 (d, 2H, J = 8.8 Hz, p-Cl-C_6H_4), 7.39 (d, 2H, J = 8.8 Hz, p-Cl-C_6H_4), 7.69 (d, 1H, CH), 8.75 (d, 1H, J = 2.0 Hz, NH). 13C-NMR δ: 53.22, 55.49, 118.83, 127.98 (2C), 128.62 (2C), 132.49, 141.99, 146.99, 151.84, 153.77. IR (υ/cm−1): 3484, 3223, 3177, 3105, 2906, 2189, 1646, 1645, 1602, 1545, 1446.

Compound -7e:
5-Amino-7-(4-nitrophenyl)-7,8-dihydro-[1,2,4]-triazolo[4,3-a]pyrimidine-6-carbonitrile.
Brown powder; mp = 245−247 °C. 1H-NMR δ: 5.46 (d, 1H, CH), 7.23 (s, 2H, NH_2), 7.46 (d, 2H, J = 8.8 Hz, p-O_2N-C_6H_4), 7.65 (d, 1H, CH), 8.16 (d, 2H, J = 8.2 Hz, p-O_2N-C_6H_4), 8.85 (d, 1H, J = 2.0 Hz, NH). 13C-NMR δ: 53.15, 54.79, 118.68, 124.02 (2C), 127.30 (2C), 147.06, 147.15, 150.11, 151.96, 153.75. IR (υ/cm−1): 3416, 3259, 3085, 2197, 1685, 1619, 1526, 1479, 1335, 1145.

Compound -7f:
5-amino-7-(isoquinolin-5-yl)-7,8-dihydro-[1,2,4]triazolo[4,3-a]pyrimidine-6-carbonitrile; White powder; mp = 241−243 °C. 1H-NMR δ: 4.96 (d, 1H, CH), 7.52(s, 2H, NH_2), 7.35 (d, 2H, J = 8.8 Hz,), 7.37 (t, 1H, CH), 7.71 (d, 1H, J = 8.2 Hz), 7.60(d, 1H, CH), 8.72 (d, 1H, J = 2.0 Hz, NH). 13C-NMR δ: 52.3, 71.2, 116.8, 119.5, 127.5, 130.2, 131.7, 132.5, 134.7, 140.7, 156.2, 157.5. IR (υ/cm−1): 3427, 3247, 3078, 2188, 1692, 1626, 1518, 1485, 1349, 1153.

CONCLUSION

In conclusion, we have described a convenient route to multi-substituted triazolopyrimidines from a three component condensation of 3-amino-[1,2,4]-triazole, aromatic aldehyde and malononitrile. The present method carries the advantage, not only the reaction performed is rapid, but also efficient in its yield. The procedure mentioned here provides an acceptable one-pot method for the preparation of multi-substituted triazolopyrimidines.

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