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Multi-component reaction to access a library of polyfunctionally substituted 4,7-dihydropyrazolo[3,4-*b*]pyridines

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ABSTRACT

A practical approach to polyfunctionally substituted 4,7-dihydropyrazolo[3,4-*b*]pyridine derivatives from heteroaryl hydrazine, 3-aryl-3-oxopropanenitriles and aldehydes have been described in the report. The present catalyst-free protocol involves the intermediacy of 5-aminopyrazole and α-cyanochalcone, which undergoes *in situ* Michael addition to afford title compounds in moderate to good yields. All the steps were conducted concomitantly to render the procedure as practical and straightforward as possible. The expeditious synthetic protocol experiment takes less than one hour and shows broad substrate scope.

ARTICLE HISTORY
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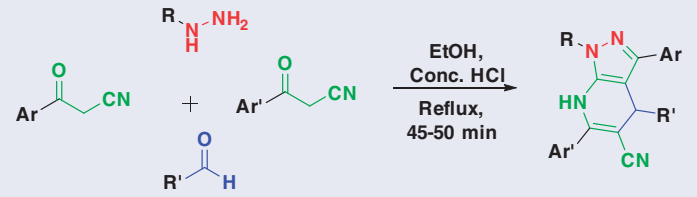
KEYWORDS
Aldehydes; 4,7-dihydropyrazolo[3,4-b]pyridines; heteroarylhydrazines; multi-component reaction; 3-oxo-3-arylpropanenitriles

GRAPHICAL ABSTRACT



- ✓ Metal free
- ✓ Broad substrate scope
- ✓ Simple efficient practical experimental procedure
- ✓ Green multi-component strategy

Introduction

Azaheterocycles are ubiquitous scaffolds in pharmaceuticals, natural products, and biologically active compounds. Pyrazolo[3,4-*b*]pyridine system, in particular, constitutes a privileged substructure and has gained special attention of the researchers in the last few decades. These compounds have been reported to exhibit antimicrobial,[1,2] anti-inflammatory,[3,4] A1 adenosine receptor inhibitor,[5] anticancer,[6,7] glycogen synthase

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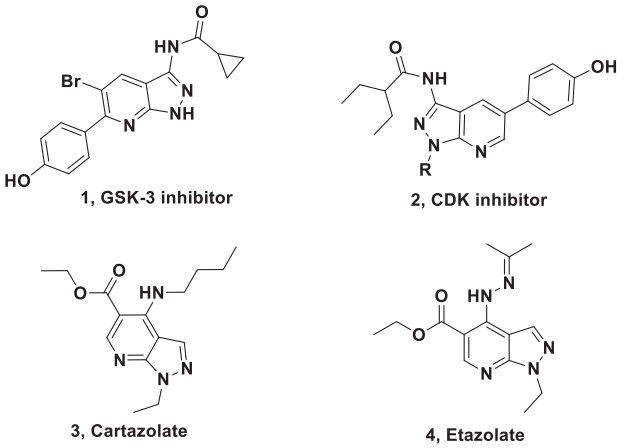


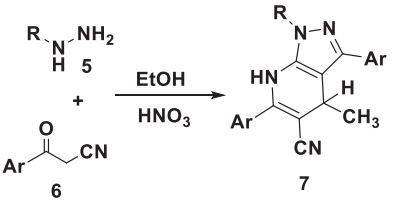
Figure 1. Representatives drugs and bioactive pyrazolo[3,4-*b*]pyridines.

kinase-3[8,9] (**1**, Figure 1), inhibitors of cyclin-dependent protein kinase-2 (cdk-2) (**2**, Figure 1),[10] antiplatelet,[11] and human nicotinamide phosphoribosyltransferase (NAMPT) inhibitor[12] activities. These compounds have also been demonstrated as promising pharmaceuticals in the treatment of anxiety,[13] depression,[14] schizophrenia and Alzheimer's disease.[3,15] Cartazolate and Etazolate (**3** and **4,** respectively, Figure 1) are two of the marketed drugs having pyrazolo[3,4-*b*]pyridine nucleus, being used for their anxiolytic activity.

Moreover, its 4,7-dihydro derivative is also emerging as a privileged heterocyclic scaffold known for its biological and pharmaceutical potency[6,16] and is reported to exhibit anti-cancer[17] and vasodilating activities.[18] The saturated carbon in the nuclear frame of 4,7-dihydropyrazolo[3,4-*b*]pyridine derivative brings an additional non-linear dimensional feature to the scaffold thus making it a better pharmacophore than its planar aromatic counterpart.

Although a variety of methods are used to prepare pyrazolo[3,4-*b*]pyridines[19–24], the synthetic access to polysubstituted-polyfunctionalized derivatives remains a serious challenge. Among the reported methods, the reaction between 5-aminopyrazoles and bielectrophiles seems to be the most prevalent method.[25] Moreover, isolation of its dihydro derivative, 4,7-dihydropyrazolo[3,4-*b*]pyridine is reported only in few cases.[26,27] Kolosov et al.[28] utilized a two step synthetic procedure which involved the synthesis of intermediate α-cyanochalcones and their subsequent condensation with phenylhydrazine. Recently, M. D. Hill[29] reported a three-component synthesis involving the reaction of 5-aminopyrazoles, 3-oxopropanenitriles and aldehydes in DMF for 16 hours. However, all these synthetic protocols employ lengthy procedures, harsh reaction conditions, e.g. additives and catalysts moreover, setting up of polyfunctional groups on the nucleus is particularly difficult.

Meanwhile, multi-component reactions are one such synthetic strategy which can be employed for diversity-oriented target synthesis in fewer synthetic steps and short reaction time.[30–32] Such reactions provide improved yields and structural diversity in economical reaction conditions.[33] Multi-component reactions (MCRs) are becoming more prevalent over conventional linear-type syntheses due to associated significant



Scheme 1. Recently reported reaction of aryl/heteroarylhydrazines with 3-oxo-3-arylpropanenitriles.

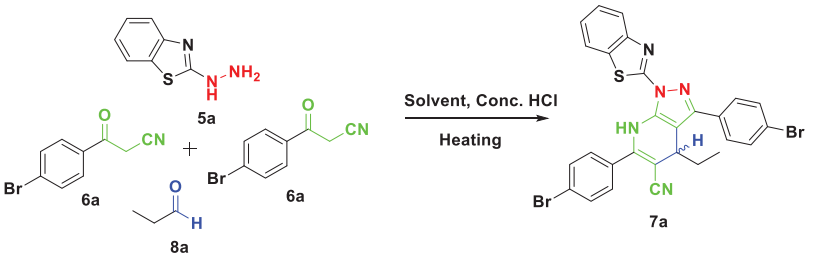
advantages in organic and medicinal chemistry particularly for the generation of diverse chemical libraries having drug-like features.[34,35] In recent years, we have developed several fused pyrazole derivatives including pyrazolo[3,4-*b*]pyridines using MCRs.[36,37]

Recently, we have reported that the reaction of aryl/heteroaryl hydrazine (**5**) with 3-oxo-3-arylpropanenitrile (**6**) in the presence of conc. HNO_3 which resulted in an unexpected formation of 4,7-dihydropyrazolo[3,4-*b*]pyridine (**7**) (Scheme 1).[38] The structure was confirmed by using several spectroscopic techniques like mass spectrometry, IR, NMR (^{1}H and ^{13}C), HMBC and x-ray crystallographic studies. The mechanistic study of the reaction revealed that there is *in situ* oxidation of ethanol to acetaldehyde by conc. HNO_3 which turns the reaction into a multi-component assembly where acetaldehyde serves as one of the reactants (Scheme 1). The fascinating results[38] of the reaction inspired us to expand the scope of the reaction using different heteroaryl hydrazine, two moles of same or one mole of each different *β*-ketonitriles with aliphatic/aromatic aldehydes (added externally) for the formation of densely substituted novel 4,7-dihydropyrazolo[3,4-*b*]pyridines bearing heteroaryl, aryl, alkyl at 1,3,4 and 6 positions. Moreover, the nitrile groups at position-5 can be explored further for conversion into amide, acid, carbonyl groups to generate more functionalized dihydropyrazolopyridines.

Results and discussion

In our initial attempts, a reaction of (benzo[*d*]thiazol-2-yl)hydrazine (**5a**) with equimolar amount of 3-oxo-3-(4-bromophenyl)propanenitrile (**6a**) and propionaldehyde (**8a**) was carried out in ethanol in the presence of two drops of conc. HCl at reflux temperature (Scheme 2).

Regular monitoring of the reaction by TLC indicated the consumption of reactants and development of a new spot. Completion of the reaction was observed in 45 minutes with the separation of a solid product in the reaction mixture. Filtration of the solid product from reaction mixture provided **7a** in 43% yield. The solid product **7a**, thus obtained was characterized by IR, ^{1}H, ^{13}C and HMBC-HSQC spectroscopic data. The IR spectrum of the compound **7a** exhibited two characteristic absorption bands at 2208 and 3340 cm^{-1} corresponding to –CN and –NH groups respectively. Formation of dihydro derivative **7a** was confirmed by the appearance of a distinct triplet at δ 4.45 ppm corresponding to 4-H and characteristic splitting pattern for ethyl group with signal of CH_3 protons appearing as triplet at δ 0.88 ppm and CH_2 protons as multiplet at δ 1.80 ppm, along with the signals corresponding to benzothiazolyl group and two aryl



Scheme 2. Synthesis of 1-(benzo[*d*]thiazol-2-yl)-3,6-bis(4-fluorophenyl)-4-methyl-4,7-dihydro-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile **7a** in ethanol by four component reaction.

substituents in aromatic region. A total of 21 signals appeared in ^{13}C spectrum of a solid product which included the signal for 1° carbon CH_3 at δ_C 8.8 ppm, 2° carbon CH_2 at δ_C 28.2 ppm and 3° carbon 4-C at δ_C 36.6 ppm. The structure was further confirmed using HMBC NMR (2D) spectroscopy where the correlation between CH_3 (δ_H 0.87–0.90 ppm) protons with 2° carbon CH_2 (δ_C 28.2 ppm) and 3° carbon 4-C (δ_C 36.6 ppm) were established. Correlations of CH_2 protons (δ_C 1.71-1.89 ppm) of ethyl group with four carbon atoms with 1° methyl carbon (δ_C 8.8 ppm), one 3° carbon 4-C (δ_C 36.6 ppm), two quaternary carbons 5-C (δ_C 84.6 ppm) and 9-C (δ_C 99.3 ppm) were also observed. In addition, the correlation of 4-H (δ_C 4.44–4.46 ppm) with seven carbons viz. CH_3, CH_2, CN (δ_C 121.7 ppm), 5-C, 6-C (δ_C 132 ppm), 9-C and 8-C (δ_C 148 ppm) and correlations of 7-H (δ_C 9.1 ppm) with five carbon atoms viz. 5-C, 6-C, 8-C, 9-C and 1′-C (4-bromophenyl) (δ_C 121.9 ppm) were also seen in the spectrum. All observed correlations established the structure of the solid product as 1-(benzo[*d*]thiazol-2-yl)-3,6-di(4-bromophenyl)-4-ethyl-4,7-dihydro-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (**7a**) (Figure 2).

To improve the low yield of the 4,7-dihydropyrazolo[3,4-*b*]pyridine **7a**, we attempted the reaction of two moles of 3-oxo-3-(4-bromophenyl)propanenitrile **6a** with one mole each of benzothiazolyl hydrazine **5a** and propionaldehyde **8a**, which resulted in considerable increase in yield from 43 to 62%. On getting successful results, we next planned to study the effect of solvent on the reaction yield in various polar and protic solvents. The results of the solvent screening are summarized in Table 1. Though the reaction has been reported in high boiling polar solvents e.g. DMSO,[39] DMF,[27] acetic acid[21] etc. in some of the literature reports, but we avoided their use due to difficulty in their vacuum elimination. From the Table 1, it may be concluded that ethanol is optimal solvent for this four component condensation which afforded significant yields (62%) of 1-(benzo[*d*]thiazol-2-yl)-3,6-di(4-bromophenyl)-4-methyl-4,7-dihydro-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile **7a** at reflux temperature in short time (Table 1, entry 2). It is worth mentioning that reaction also worked well in other homologous alcohols like methanol, propanol, and isopropanol with slightly lower yields (53, 48, and 44%, respectively) (Table 1, entries 1,3,4). However, 5-aminopyrazole was the major product when reactions were carried in polar aprotic solvents or under solvent-free conditions (Table 1, entries 5–9).

To examine the efficiency of this new multi-component reaction to synthesize various 1-(hetroaryl)-4,7-dihydro-3,6-diaryl-4-aryl/alkyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-nitriles, **7a–i**,

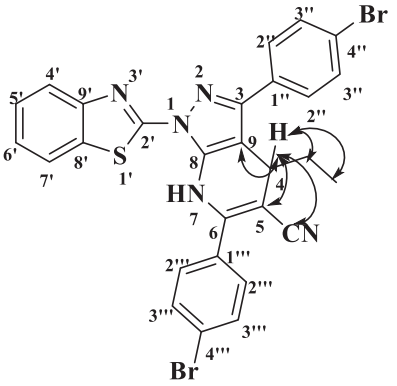
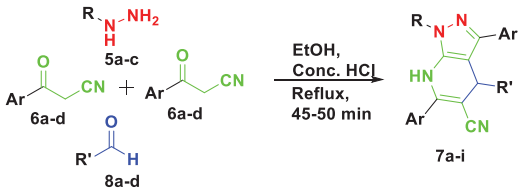


Figure 2. Significant correlations observed in HMBC data of compound **7a**.

Table 1. Reaction profile of Solvent screening for synthesis of compound **7a**.

Entry	Solvent	Temperature	Product	Time (min)	Isolated Yield (%)
1	Methanol	65 °C	4,7-dihydropyrazolo[3,4-*b*]pyridine	45–50	53
2	Ethanol	78 °C	4,7-dihydropyrazolo[3,4-*b*]pyridine	45–50	62
3	Propanol	97 °C	4,7-dihydropyrazolo[3,4-*b*]pyridine	60–65	48
4	Isopropanol	83 °C	4,7-dihydropyrazolo[3,4-*b*]pyridine	60–65	44
5	Chloroform	62 °C	5-aminopyrazole	180	35
6	Acetonitrile	82 °C	5-aminopyrazole	180	65
7	Dioxane	101 °C	5-aminopyrazole	180	45
8	THF	66 °C	5-aminopyrazole	180	52
9	Solvent free	rt	5-aminopyrazole	20	82

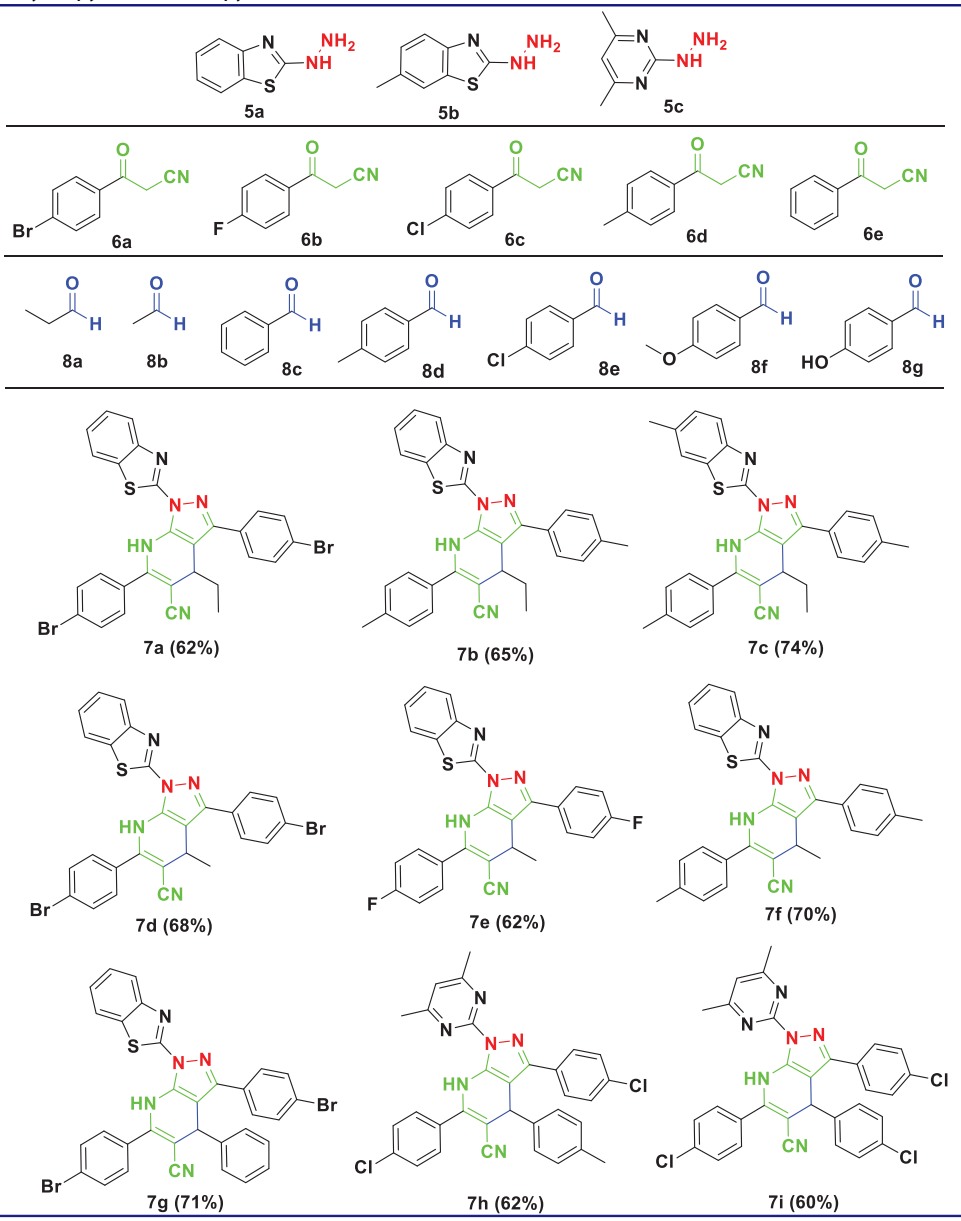


Scheme 3. General route for the synthesis of novel 4,7-dihydropyrazolo[3,4-*b*]pyridines **7a-i**.

a series of different aldehydes were employed (Scheme 3). As seen in Table 2, this protocol can be employed to aliphatic (CH_3, CH_3CH_2) and aromatic aldehydes bearing electron donating groups as well as electron withdrawing groups. Furthermore, the substrate scope was explored by employing various heteroaryl hydrazine (**5a–c**) and 3-aryl-3-oxopropanenitriles (**6a–d**). Improved yield was obtained when 6-methylbenzo[*d*]thiazolylhydrazine, **5 b**, was used with 3-(4-tolyl)-3-oxopropanenitrile **8d**, and propionaldehyde **8a**, for the synthesis of 4,7-dihydro-1H-pyrazolo[3,4-*b*]pyridine, **7c**, (74% yield). The reaction of 4-chlorobenzaldehyde (**8e**) and 4-methylbenzaldehyde (**8d**) with 4,6-dimethylpyrimidin-2-ylhydrazine (**5c**) and 3-(4-chlorophenyl)-3-oxopropanenitrile (**6c**) afforded corresponding 4,7-dihydropyrazalo[3,4-*b*]pyridines in 62% (**7h**) and 60% (**7i**) yields, respectively.

Encouraged by the success of our protocol, the scope of the methodology was further investigated in the reactions with heteroaryl hydrazine (**5a–c**), two different 3-oxopropanenitriles (**6a–e**) and various aldehydes (**8a–f**) so as to achieve 4,7-dihydropyrazolo[3,4-*b*]pyridines (**7j–r**) with non-identical aryl groups at 3 and 6 positions. The model

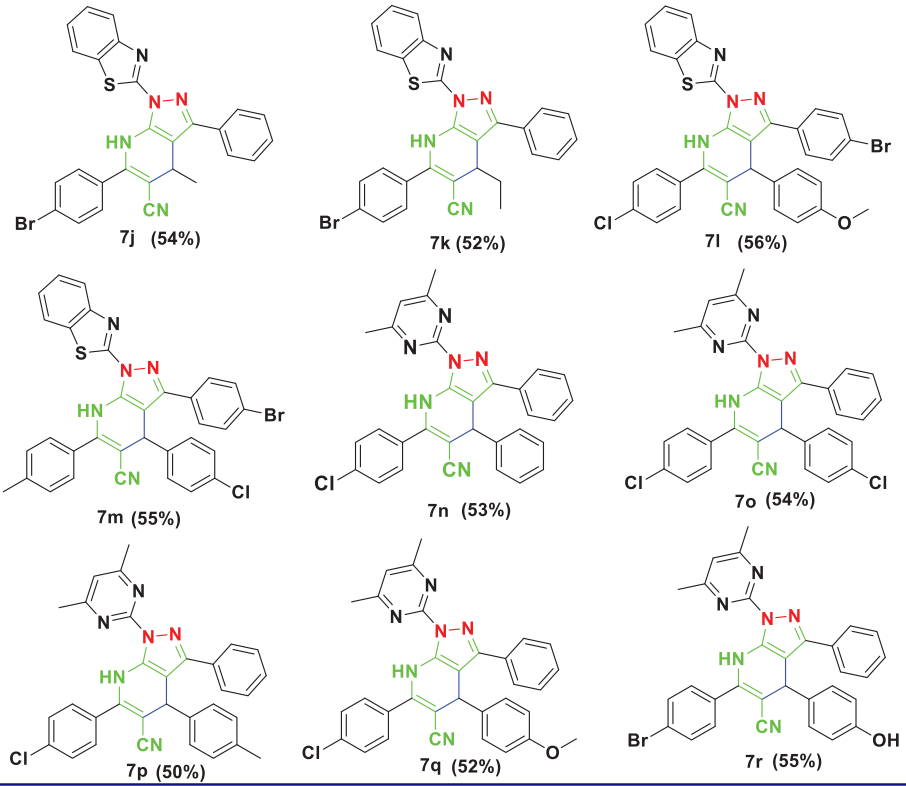
Table 2. Scope of heteroarylhydrazines **5a-c**, 3-aryl-3-oxopropanenitriles **6a-e**, aldehyde **8a-g** and 4,7-dihydropyrazolo[3,4-*b*]pyridine derivatives **7a-i**[a].



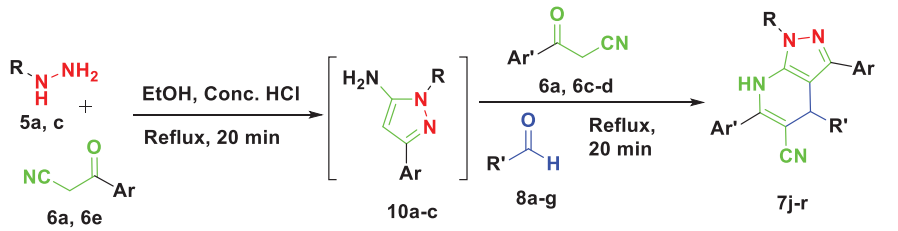
[a]Isolated yield.

reaction was carried out with sequential addition of reactants by refluxing the mixture of benzo[*d*]thiazolylhydrazine (**5a**) and 3-phenyl-3-oxopropanenitrile (**6e**) for 20 minutes (Scheme 4). On completion of the reaction, 3-(4-bromophenyl)-3-oxopropanenitrile (**6a**) and acetaldehyde (**8b**) were added subsequently to the refluxing reaction mixture and heated for another 20 minutes. 1-(Benzo[*d*]thiazol-2-yl)-6-(4-bromophenyl)-4-methyl-3-phenyl-4,7-dihydropyrazolo[3,4-*b*]pyridine-5-carbonitrile (**7j**) was isolated in a

Table 3. Substrate scope for the preparation of 4,7-dihydropyrazolo[3,4-*b*]pyridine derivatives[a] **7j-r**.



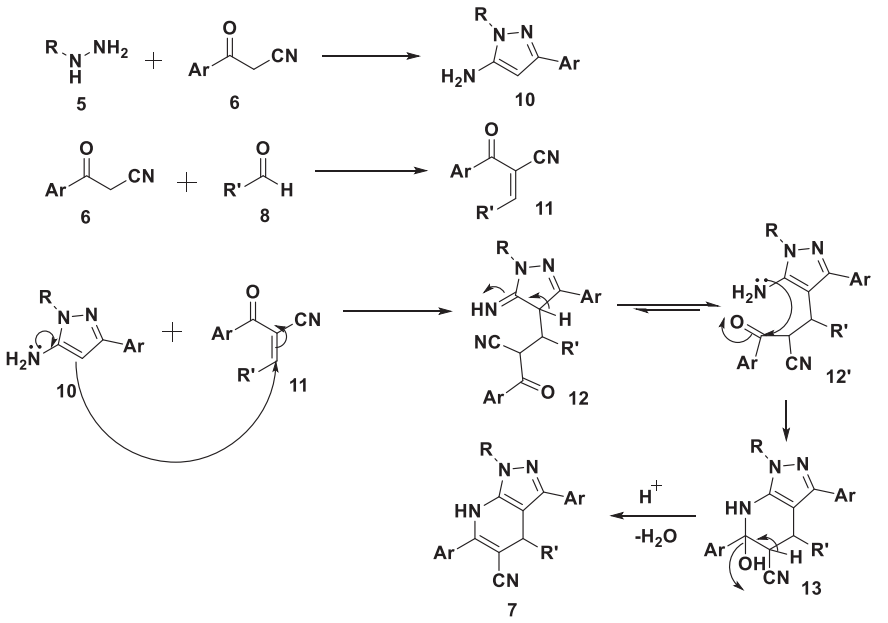
[a]Isolated yield.



Scheme 4. Synthesis of unsymmetrically substituted 4,7-dihydropyrazolo[3,4-*b*]pyridines **7j-r**.

modest 54% yield. Further, the same reaction was extended to incorporate ethyl group on 4,7-dihydropyrazolo[3,4-*b*]pyridine nucleus by replacing the acetaldehyde with propionaldehyde **8a**. The reaction substrate scope was further extended to various aromatic aldehydes (**8c–f**), 3-oxopropanenitriles (**6a–e**) and heteroaryl hydrazines (**5a–c**) as shown in Table 3. The reaction yields depend on the substrate diversity but still, it can be generalized that in all the cases yields in sequential addition reaction were slightly lower (45–50%) than the former multi-component reactions (60–70%).

The structural characterization of products was carried out by IR, ^{1}H & ^{13}C NMR spectroscopy and mass spectrometry.



Scheme 5. Plausible mechanism for the formation of 4,7-dihydropyrazolo[3,4-*b*]pyridine-6-nitriles **7**.

The plausible mechanism depicted in Scheme 5 may involve the following tandem reaction steps:

i. Formation of 5-aminopyrazole **10**, by reaction between heteroaryl hydrazine 5 and one mole of 3-oxo-3-arylpropanenitrile **6.**
ii. Knoevenagel condensation between aldehyde **8** and another mole of 3-oxo-3-arylpropanenitrile **6** afford α-cyanochalcone **11**.
iii. *In situ* Michael addition of 5-aminopyrazole **10** and α-cyanochalcone **11** followed by cyclization and dehydration to give 4,7-dihydropyrazolo[3,4-*b*]pyridine **7** (Scheme 5).

Conclusions

In conclusion, one step multi-component reaction of structurally diverse aldehydes, hydrazines, and 3-oxopropanenitriles resulted in the formation of polyfunctionalized 4,7-dihydropyrazolo[3,4-*b*]pyridines. The protocol has the merits of being environmentally friendly, economical, simple in operation having the easy work-up procedure, with good to moderate yields. To the best of our knowledge, this is the first report on the synthesis of 4,7-dihydropyrazolo[3,4-*b*]pyridines in one step by the four-component reaction. The dehydrogenative oxidation of corresponding 4,7-dihydropyrazolo [3,4-*b*]pyridine derivatives to corresponding pyrazolo[3,4-*b*]pyridines will be presented in due course.

Experimental section

General

Commercial solvents and other reagents were used as purchased without any purification. Melting points were determined in open capillaries on digital Melting Point Apparatus (MEPA), Lab India and were uncorrected. IR spectra were recorded on Buck Scientific IR M-500 spectrophotometer using KBr pellets (ν_{max} in cm^{-1}), ^{1}H and ^{13}C NMR spectra on a Bruker instrument at 400 and 100 MHz, respectively, using deuteriochloroform as a solvent. (^{1}H-^{13}C) gs-HMQC, (^{1}H-^{13}C) and gs-HMBC, of compound 7a, were acquired on a Bruker DRX 400 (9.4 Tesla, 400 MHz for ^{1}H and 100 MHz for ^{13}C) spectrometer with a 5 mm inverse-detection H-X probe equipped with a z-gradient coil, at 300 K and processed using standard Bruker NMR software and in non-phase-sensitive mode. Gradient selection was achieved through a 5% sine truncated shaped pulse gradient of 1 ms. Elemental analyses were performed at Sophisticated Analytical Instrument Facility, Panjab University, Chandigarh. All the compounds gave C, H, and N analysis within ±0.5 of the theoretical values.

Synthesis

Heteroarylhydrazines 5 and 3-aryl-3-oxopropanenitriles **6** were prepared according to literature procedures.[40–43]

Synthesis of 1-(Benzo[*d*]thiazol-2-yl)-4,7-dihydro-4-ethyl-3,6-di(4-bromophenyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-nitrile (7a). To a solution of 0.45 g of 3-(4-bromophenyl)-3-oxopropanenitrile (**6a**, 2.0 mmol) in 25 mL of ethanol, 0.165 g of benzothiazolylhydrazine (**5a**, 1.0 mmol) and 0.058 g of propionaldehyde (**8a**, 1.0 mmol) were added along with 2 drops of conc. HCl. The reaction mixture was heated to reflux for 45 minutes until the formation of a solid product in the reaction mixture. The hot reaction mixture was filtered at the vacuum pump and washed with hot ethanol to afford the pure compound **7a**.

All other compounds (**7b–i**) were synthesized according to the procedure mentioned for **7a** using heteroarylhydrazines (**5a–c**), different 3-aryl-3-oxopropanenitriles (**6a–d**) and aldehydes (**8a–d**).

1-(Benzo[*d*]thiazol-2-yl)-4,7-dihydro-4-ethyl-3,6-di(4-bromophenyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-nitrile (7a). Yield 62%; M.p. 240–245 °C; IR (KBr, cm^{-1}): 2208 (C≡N), 3340 (N–H); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87–0.90 (t, 3 H, CH_3, J 6.8 Hz), 1.71–1.89 (m, 2 H, CH_2), 4.44–4.46 (t, 1 H, 4-H, J 4 Hz), 7.38–7.42 (m, 1 H, 6'-H), 7.48–7.51 (m, 1 H, 5′-H), 7.62–7.69 (m, 6 H, Ph-H), 7.72–7.74 (m, 2 H, 2"-H), 7.78–7.80 (d, 1 H, 7′-H, J 8.0 Hz), 7.86–7.88 (d, 1 H, 4′-H, J 8.0 Hz), 9.1 (s, 1 H, exchangeable with D_2O, 7-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 8.8, 28.2, 36.6, 84.7, 99.5, 121.7, 121.9, 123.4, 125.1, 125.4, 126.8, 128.7, 129.3, 130.9, 131.5, 132.0, 132.6, 139.9, 148.4, 150.3, 160.7; MS: m/z 615.97 $[M+1]^+$, 617.97 $[M+1+2]^+$, 619.97 $[M+1+4]^+$, (1:2:1); Elemental analysis: Calcd. for $C_{28}H_{19}Br_2N_5S$: C, 54.47; H, 3.10; N, 11.34; Found: C, 53.35; H, 2.63; N, 11.12.

Synthesis of 1-(benzo[*d*]thiazol-2-yl)-6-(4-bromophenyl)-4-methyl-3-phenyl-4,7-dihydro-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (7j). The solution of 0.145 g 3-

phenyl-3-oxopropanenitrile (**6e** 1.0 mmol) in 25 mL of ethanol and 0.165 g benzothiazolylhydrazine (**5a**, 1 mmol) was refluxed for 20 minutes in the presence of conc. HCl. The progress of the reaction was monitored by TLC (ethyl acetate/n-hexane: 1/4). After complete consumption of reactants, the reaction mixture was added with 0.225 g 3-(4-bromophenyl)-3-oxopropanenitrile (**6a**, 1 mmol) and 0.044 g acetaldehyde (**8 b**, 1 mmol). The reaction mixture was heated again to reflux for another 20 minutes till solid product separates out in the reaction mixture. The reaction mixture was filtered at the vacuum pump and washed well with hot ethanol to afford the pure **7j**.

Compounds (**7k–r**) were synthesized using the same procedure with sequential addition of appropriate reactants.

1-(benzo[*d*]thiazol-2-yl)-6-(4-bromophenyl)-4-methyl-3-phenyl-4,7-dihydro-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (7j). Yield 54%; M.p. 250–255 °C; IR (KBr, cm^{-1}): 3321 (N–H), 2212 (–C≡N); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.43–1.45 (d, 3 H, CH_3, J 6.8 Hz), 4.30–4.39 (q, 1 H, J 6.0 Hz), 7.21 (m, 1 H, 6′-H), 7.29–7.33 (m, 1 H, 5'-H), 7.35–7.38 (t, 1 H, 7'-H, J 6.6 Hz), 7.42–7.50 (m, 3 H, 2‴-H, 4′-H), 7.61–7.63 (d, 2 H, 3‴-H, J 8.4 Hz), 7.68–7.72 (m, 2 H, 3"-H), 7.74–7.79 (m, 2 H, 2"-H), 7.82-7.85 (m, 1 H, 4'-H), 9.04 (s, 1 H, –7-NH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 23.7, 31.2, 87.1, 102.0, 121.7, 121.9, 124.9, 126.7, 127.1, 128.4, 128.8, 129.1, 129.3, 132.5, 150.4. MS: *m/z* 538.12 $[M+1]^+$, 540.18 $[M+1+2]^+$, (1:1); Elemental analysis: Calcd. for $C_{28}H_{20}BrN_5S$: C, 62.46; H, 3.74; N, 13.01; Found: C, 62.19; H, 3.53; N, 12.87.

Full experimental details, ^{1}H and ^{13}C NMR spectra can be found in supplementary content section of this article's webpage.

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