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Facile Synthesis of 5-Substituted Pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidines and Pyrazolo[4,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidines

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Abstract: The bicyclic fused heterocycle pyrazolo[3,4-*d*]pyrimidines were extended to tricyclic fused heterocycle pyrazolo[4,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidines (PTP1s) in two steps synthesis by cyclization of 4-hydrazinyl-1*H*-pyrazolo[3,4-*d*]pyrimidines with formic acid under conventional heating. The PTP1s easily undergo Dimroth rearrangement to yield another isomeric pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidines (PTP2s). A systematic study of solvent effect on Dimroth rearrangement showed that the rearrangement is depend on polarity of solvent and nature of nucleophile used. Purine analog of pyrazolo[4,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidine was also synthesized. This method offers several advantages such as excellent yields (87-94%), mild reaction condition and simple work-up.

Keywords: Pyrazolo[4,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidines, pyrazolo[4,3-*e*][1,2,4]triazolo-[1,5-*c*]pyrimidines, 9*H*-[1,2,4]triazolo[4,3-*i*]purine, Dimroth rearrangement.

Introduction

Intervention with cell cycle is an attractive strategy for combating microbes as well as diseases associated with abnormal cellular proliferation like cancer [1] and DNA is one of the promising targets in this field. A planar or semi-planar pharmacophore with a polyaromatic ring, capable of intercalation into DNA, is the common characteristic feature of

DNA-intercalating anticancer drugs. Many of such intercalators, found in literature have tricyclic ring system [2]. In addition, protein kinases are involved in regulation of all cell functions. Uncontrolled activation of many of these kinases has been shown to result in uncontrolled cell growth. Based on literature reports, fused tricyclic core systems have been used as scaffold for kinase inhibitors [3-4]. Pyrazolo-triazolopyrimidines are a

class of fused heterocycles interesting from the view point of pharmacological activities [5-8]. Pyrazolo[4,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidine (**PTP1**) derivatives have been found to be highly potent and selective human A_{2A} , A_{2B} and A_3 adenosine receptor antagonists [3]. Efforts made in medicinal chemistry in the past few decades have revealed that the isomeric ring system pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine (**PTP2**) is one of the structural requirements for compounds that behave as selective antagonists for human A_{2A} and A_3 adenosine receptor subtypes [9]. The **PTP1** and **PTP2** ring systems have not received much attention and very little is known about the synthesis and properties of these compounds. Prompted by these findings and due to our interest in heterocycles we report herein a convenient synthesis of some new **PTP1s 3a–3c** that might be of pharmacological importance. We utilised pyrazolo[3,4-*d*]pyrimidine derivatives as starting material for the synthesis of **PTP1s**. The synthesis was involved two steps with good yields and easy work up. Furthermore, attempts to prepare the isomeric pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine (**PTP2**) via dehydrative cyclization of the 4-acylhydrazino-pyrazolo[3,4-*d*]pyrimidines [10] or via Dimroth rearrangement of **PTP1** in presence of base were reported to give the corresponding **PTP2** [11]. However, the role of solvent and nucleophile are not studied till now for such synthesis. We have prepared **PTP2s** by Dimroth rearrangement of **PTP1s** and systematically studied the role of solvent and nucleophile on the rearrangement.

Experimental

General Chemistry: Melting points are uncorrected and were determined in capillary tubes on a precision melting point apparatus containing silicon oil. ^1H NMR and ^{13}C NMR spectra were recorded either on a Bruker DPX-200 or Bruker Advance DRX-300 FT spectrometers. NMR spectra were recorded

on 300 MHz spectrometers for ^1H NMR and 50, 75 and 100 MHz for ^{13}C NMR in CDCl_3 or $\text{DMSO-}d_6$ with TMS as internal reference wherever mentioned. Chemical shifts (δ) are reported in parts per million (ppm) for ^1H and ^{13}C NMR spectra. Coupling constants J are reported in hertz (Hz). Multiplicities are reported as follows: singlet (s), broad (br), doublet (d), triplet (t), quartet (q), and multiplet (m). The HRMS spectra were recorded as ESI-HRMS on Agilent 6520 Q-TOF, LC-MS/MS mass spectrometer. The reaction progress was routinely monitored by thin-layer chromatography (TLC) on precoated silica gel plates. Column chromatography was performed over silica gel (60-120 mesh) size. The room temperature varied between 20 °C to 35 °C. All the solvents and chemicals were used as procured from the suppliers.

General procedure for the preparation of 5-(alkylsulfanyl)-7H-pyrazolo[4,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidines (3). To a suspension of 4,6-dialkylsulfanyl-1H-pyrazolo-[3,4-*d*]pyrimidine (**1**) (4.4 mmol) in ethanol (15 mL) was added hydrazine hydrate (1.28 mL, 26.4 mmol) and the mixture was refluxed for 3-4 h. After completion of the reaction, cooled reaction mixture on ice-bath and allowed to precipitate for an hour. The precipitate was filtered and washed with alcohol followed by ether to get pure intermediate **2**. The intermediate **2** was dissolved in 10 mL of formic acid and reaction mixture was refluxed for one hour. After completion of reaction the volatile materials were removed under reduced pressure. Residue was poured in 100 mL of cold water and extracted with chloroform (3 × 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification by crystallization in mixture of chloroform and ethyl acetate gave pure **3**.

7-Methyl-5-methylsulfanyl-7H-pyrazolo[4,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidine (3a): m.p. 220 °C; ^1H NMR (300

MHz, CDCl_3 , 25 °C, TMS) δ = 2.83 (s, 3 H, SMe), 4.07 (s, 3 H, NMe), 8.21 (s, 1 H, Ar-H), 8.74 (s, 1 H, Ar-H); ^{13}C NMR (75 MHz, CDCl_3 , 25°C, TMS) δ = 13.6, 34.5, 97.2, 131.8, 133.3, 143.0, 145.7, 148.6; HRMS (ESI) calcd for $\text{C}_8\text{H}_8\text{N}_6\text{S}$ $[\text{M} + \text{H}]^+$ 221.0609, found 221.0605.

5-Ethylsulfanyl 7-methyl-7H-pyrazolo[4,3-e][1,2,4]triazolo[4,3-c]pyrimidine (3b): m.p. 210 °C; ^1H NMR (300 MHz, CDCl_3 , 25°C, TMS) δ = 1.54 (t, J = 7.4 Hz, 3 H, CH_3), 3.47 (q, J = 7.4 Hz, 2 H, SCH_2), 4.09 (s, 3 H, NMe), 8.23 (s, 1 H, Ar-H), 8.74 (s, 1 H, Ar-H); ^{13}C NMR (300 MHz, CDCl_3 , 25°C, TMS) δ = 13.85, 26.20, 34.61, 97.43, 131.91, 133.52, 144.64, 145.38, 148.25; Elemental Analysis calcd for $\text{C}_9\text{H}_{10}\text{N}_6\text{S}$: C, 45.94; H, 4.71; N, 35.72; found: C, 45.90; H, 4.85; N, 35.65.

5-Methylsulfanyl-7H-pyrazolo[4,3-e][1,2,4]triazolo[4,3-c]pyrimidine (3c): m.p. 230 °C; ^1H NMR (400 MHz, $\text{DMSO}-d_6$, 25°C, TMS) δ = 2.86 (s, 3 H, SMe), 8.65 (br., s, 1 H, Ar-H), 9.45 (s, 1 H, Ar-H), 14.16 (br., s, 1 H, NH); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$, 25 °C, TMS) δ = 13.61, 96.77, 125.53, 128.06, 135.18, 144.39, 148.63; HRMS (ESI) calcd for $\text{C}_7\text{H}_7\text{N}_6\text{S}$ $[\text{M} + \text{H}]^+$ 207.0453, found 207.0475.

Synthesis of 5-ethylsulfanyl-9-methyl-9H-[1,2,4]triazolo[4,3-*i*]purine (5). To a suspension of 2,6-bisethylsulfanyl-7-methyl-7H-purine **4** (0.200 g, 0.786 mmol) in ethanol (15 mL) was added hydrazine hydrate (0.38 mL, 7.86 mmol) and the mixture was refluxed for 24 h. After consumption of the starting **4**, formic acid was added dropwise to reaction mixture and refluxing was further continued for an hour. After completion of reaction the volatile materials were removed under reduced pressure. Residue was poured in 100 mL of cold water and extracted with chloroform (3 $\times$ 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification by column chromatography in mixture of chloroform and ethyl acetate gave

pure **5**. (0.150 g, 80% yield) as a colorless solid. ^1H NMR : m.p. 230 °C; ^1H NMR (300 MHz, CDCl_3 , 25°C, TMS) δ = 1.53 (t, J = 7.3 Hz, 3 H, CH_3), 3.53 (q, J = 7.2 Hz, 2 H, SCH_2), 4.27 (s, 3 H, NMe), 7.89 (s, 1 H, Ar-H), 8.83 (s, 1 H, Ar-H); ^{13}C NMR (300 MHz, CDCl_3 , 25°C, TMS) δ = 14.31, 26.22, 34.25, 110.06, 133.62, 141.58, 142.38, 144.07, 149.28; Elemental Analysis calcd for $\text{C}_9\text{H}_{10}\text{N}_6\text{S}$: C, 45.94; H, 4.71; N, 35.72; found: C, 45.98; H, 4.80; N, 35.67.

Synthesis of 5-methoxy-7-methyl-7H-pyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidine (6a). To a suspension **3a** (0.500 g, 2.2 mmol) in methanol (15 mL) was added sodium acetate (1.082 g, 13.2 mmol) and the mixture was refluxed for 6 h. After completion of reaction the volatile materials were removed under reduced pressure. Residue was poured in 50 mL of cold water and extracted with chloroform (3 $\times$ 40 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification by crystallization in mixture of chloroform and ethyl acetate gave pure **6a** (0.370 g, 82% yield) as a colorless solid. ^1H NMR (300 MHz, CDCl_3 , 25 °C, TMS) δ = 4.06 (s, 3 H, NMe), 4.34 (s, 3 H, OMe), 8.18 (s, 1 H, Ar-H), 8.27 (s, 1 H, Ar-H); ^{13}C NMR (75 MHz, CDCl_3 , 25 °C, TMS) δ = 34.48, 56.64, 98.91, 131.78, 146.48, 148.55, 149.58, 154.14; HRMS (ESI) calcd for $\text{C}_8\text{H}_8\text{N}_6\text{O}$ $[\text{M} + \text{H}]^+$ 205.0838, found 205.0834.

Synthesis of 5-ethoxy-7-methyl-7H-pyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidine (6b). The procedure was same as used for synthesis of **6a** except ethanol was taken in the place of methanol. Yield 84% (0.480 g). ^1H NMR (300 MHz, CDCl_3 , 25 °C, TMS) δ = 1.64 (t, J = 7.1, Hz, 3 H, CH_3), 4.09 (s, 3 H, NMe), 4.84 (q, J = 7.1, Hz, 2 H, CH_2), 8.23 (s, 1 H, Ar-H), 8.30 (s, 1 H, Ar-H); ^{13}C NMR (75 MHz, CDCl_3 , 25 °C, TMS) δ = 14.04, 34.37, 66.36, 77.63, 98.73, 131.67, 146.48, 147.96, 149.50, 153.96; HRMS (ESI) calcd for $\text{C}_9\text{H}_{10}\text{N}_6\text{O}$ $[\text{M} + \text{H}]^+$ 219.0994, found 219.0986.

Synthesis of *N,N*,7-trimethyl-7*H*-pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidin-5-amine (7a). To a suspension **3a** (0.500 g, 2.2 mmol) in acetonitrile (15 mL) was added aqueous solution (40% w/v) of dimethylamine (1.7 mL, 13.2 mmol) and the mixture was refluxed for 4 h. After completion of reaction the volatile materials were removed under reduced pressure. Residue was poured in 50 mL of cold water and extracted with chloroform (3 × 40 mL). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated in vacuo. Purification by column chromatography (chloroform/EtOAc) gave **5a** 0.190 g, 85% yield); ¹H NMR (300 MHz, CDCl₃, 25 °C, TMS) δ = 3.56 (s, 6 H, 2 × NMe), 4.04 (s, 3 H, NMe), 8.36 (s, 1 H, Ar-H), 8.40 (s, 1 H, Ar-H); ¹³C NMR (75 MHz, CDCl₃, 25 °C, TMS) δ = 34.01, 40.86, 97.07, 131.57, 147.17, 148.05, 151.83; HRMS (ESI) calcd. for C₉H₁₁N₇ [M + H]⁺ 218.1154, found 218.1149.

Synthesis of 7-methyl-5-(pyrrolidin-1-yl)-7*H*-pyrazolo[4,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidine (8a) and 7-methyl-5-(pyrrolidin-1-yl)-7*H*-pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine (8b). To a suspension **3a** (0.500 g, 2.2 mmol) in acetonitrile (15 mL) was added pyrrolidine (1.8 mL, 22.0 mmol) and the mixture was refluxed for 4 h. After completion of reaction the volatile materials were removed under reduced pressure. Residue was poured in 50 mL of cold water and extracted with chloroform (3 × 40 mL). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated in vacuo. Purification by column chromatography (chloroform/EtOAc) gave **8a** (0.295 g, 55% yield) as colorless solid and **8b** (0.190 g, 35% yield) as colorless solid.

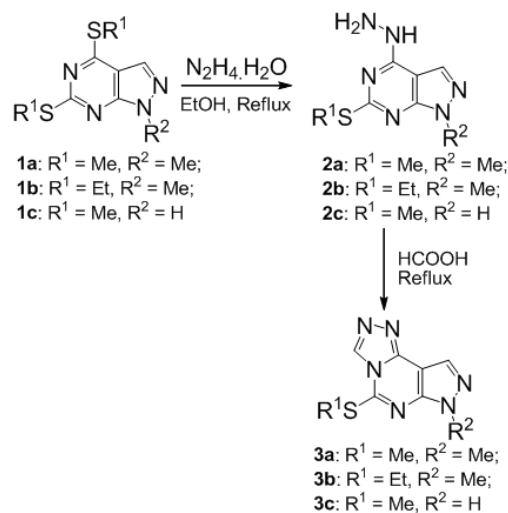
8a. ¹H NMR (400 MHz, CDCl₃, 25 °C, TMS) δ = 2.07–2.18 (m, 4 H, 2 × NCH₂), 3.94 (s, 3 H, NMe), 3.86–3.97 (m, 4 H, 2 × NCH₂), 8.11 (s, 1 H, Ar-H), 8.95 (s, 1 H, Ar-H); ¹³C NMR (101.1 MHz, CDCl₃, 25 °C, TMS) δ = 25.64, 34.10, 50.48, 95.90, 131.64, 144.77, 148.84,

151.26; HRMS (ESI) calcd for C₁₁H₁₄N₇ [M + H]⁺ 244.1311, found 244.1302.

8b. ¹H NMR (300 MHz, CDCl₃, 25 °C, TMS) δ = 1.97–2.08 (m, 4 H, 2 × CH₂), 3.94 (s, 3 H, NMe), 4.01–4.20 (m, 4 H, 2 × NCH₂), 8.04 (s, 1 H, Ar-H), 8.10 (s, 1 H, Ar-H); ¹³C NMR (101.1 MHz, CDCl₃, 25 °C, TMS) δ = 25.40, 33.88, 50.51, 95.90, 131.64, 144.77, 148.84, 151.26; HRMS (ESI) calcd for C₁₁H₁₄N₇ [M + H]⁺ 244.1311, found 244.1306.

Results and Discussion

Few synthetic routes to prepare **PTP1s** have been reported in literature [12-13] and several derivatives have been synthesized. We used 4,6-dialkylsulfanyl substituted pyrazolo[3,4-*d*]pyrimidines (**1**) as starting material [14] in two steps synthesis. In the first step hydrazine selectively replaced 4-alkylsulfanyl group to give corresponding 4-hydrazinyl-6-alkylsulfanyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (**2**) which in second step on cyclisation with formic acid gave **PTP1** in good yield (85-90%) as shown in Scheme 1.



Scheme 1. Synthesis of pyrazolo[4,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidines

The intermediates **2** are found in equilibrium

of two tautomers (Figure 1.) as shown by ^1H NMR analysis. The aromatic H-3 proton and NH proton, each of them showed two separate

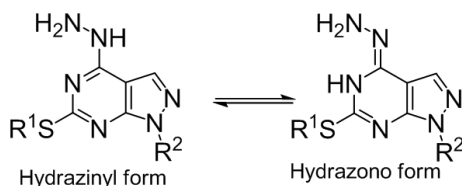


Figure 1. Tautomers of intermediates **2**

peaks, one for hydrazino tautomer and another for hydrazone tautomer as shown in Figure 2. On the basis of integration of ^1H NMR peaks the ratio of hydrazone and hydrazinyl tautomer was 3:2 (Figure 2.).

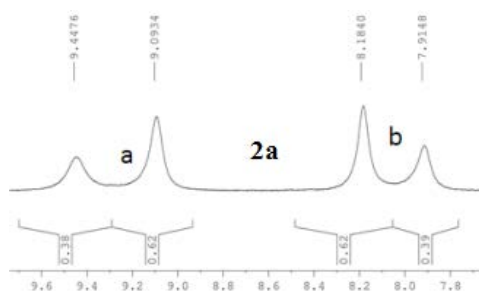
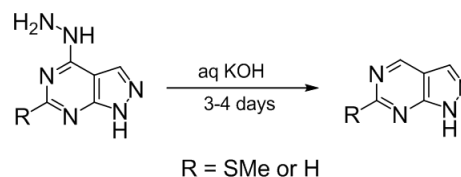


Figure 2. A portion of ^1H NMR of **2a** showing equilibrium of hydrazino and hydrazone tautomers. **a** is peak of NH and **b** is peak of aromatic H-3.

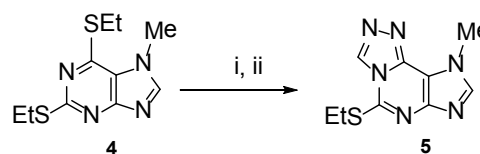
The pyrazolo[3,4-*d*]pyrimidine is isomeric with biologically important purine and also well known for its biological activity [15-16]. Since 1995 we have demonstrated use of pyrazolo[3,4-*d*]pyrimidine core for studying arene interaction both in solution and solid state [17-20]. 6-Methylsulfanyl-1*H*-pyrazolo[3,4-*d*]pyrimidine is one of the derivatives which has received much less synthetic attention and there are only few synthetic routes reported in literature. We synthesized it via a new route using intermediate **2c** (Scheme 2). Such type of reaction was reported by Temple *et al.* [21] for the first time in 1965 and later the mechanism

was proposed by Broceta *et al.* in 2007 [22]. This type of reaction is well known, but it has never been used before for the reduction/selective reduction of methylsulfanyl-containing heterocycles.



Scheme 2. Synthesis of 1*H*-pyrazolo[3,4-*d*]pyrimidines.

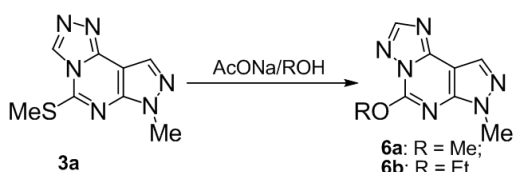
To get **PTP1** from **1**, it is not necessary to isolate intermediate **2**. In the reaction mixture, when **1** was completely consumed, formic acid was added dropwise and refluxing was further continued for an hour to yield **PTP1** in one pot synthesis. In addition we used purine analog **4** [23] as starting material to get corresponding tricyclic 9*H*-[1,2,4]triazolo[4,3-*i*]purine as shown in Scheme 3.



Scheme 3. Reagents and conditions: i- Hydrazine hydrate in ethanol, reflux, 24 h; ii- formic acid, reflux, 1h.

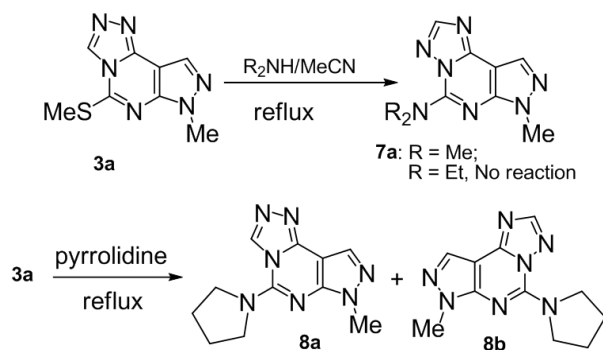
On treatment with sodium acetate in alcohol **PTP1** gave **PTP2** (Scheme 4.) via Dimroth rearrangement. According to the earlier reported mechanism [13], in Dimroth rearrangement, base attacks at fifth position of **PTP1** ring to give unstable intermediate which recycles to give rearranged **PTP2**. Since none of the 5-substituted derivatives of **PTP2s** have been prepared up to now, we became interested to prepare **PTP2** derivatives having group at 5-position. The methylsulfanyl group is better leaving group as compared to methoxy group,

therefore when **3a** was refluxed in methanol in the presence of sodium acetate it gave rearranged **6a** having expected methoxy group at 5-position. The same reaction was carried out in ethanol, n-propanol and iso-propanol but reaction proceeded only in ethanol to give product **6b**; while in propanol starting **3a** was recovered as such.



Scheme 4. Synthesis of pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidines from pyrazolo[4,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidine.

We generalized the above rearrangement with amines. On treatment with aqueous *N,N*-dimethylamine **3a** gave rearranged product **7a** whereas *N,N*-diethylamine did not react. Surprisingly, on heating **3a** in neat pyrrolidine **PTP1** did not rearranged to corresponding **PTP2**, however, methylsulfonyl group was replaced by pyrrolidinyl group. In the presence acetonitrile/propanol as solvent pyrrolidine on reaction with **3a** gave both normal product **8a** and rearranged product **8b**.



Scheme 4. Dimroth rearrangement in the presence of amines.

The rearranged and normal product ratio in different reaction conditions given by **3a** is

given in Table 1.

Table 1. Product formation in different reaction conditions.

S. No.	Reaction condition	Rearranged Product	Normal Product
1	AcONa in MeOH	6a (90%)	Not formed
2	AcONa in EtOH	6b (88%)	Not formed
3	AcONa in propanol	No reaction	
4	Me ₂ NH in MeCN	7a (80%)	Not formed
5	Et ₂ NH in MeCN	No reaction	
6	Pyrrolidine in n-Propanol	8b (58%)	8a (28%)
7	Pyrrolidine in Acetonitrile	8b (35%)	8a (55%)
8	Pyrrolidine	8b (1-2%)	8a (85%)

The mechanism of the rearrangement of **PTP1** to **PTP2** as proposed by Shawali *at. al.* is shown in Figure 3 [12]. In the presence of sodium acetate in alcohol (methanol or ethanol) 5-methylsubstituted **PTP1** completely rearranged to give corresponding **PTP2**. The aqueous *N,N*-dimethylamine in acetonitrile also gave rearranged product; while the neat pyrrolidine gave almost only without rearranged product. The one of the reasons for the formation of rearranged or without rearranged product may be that the extent of solvation of intermediate **9** and **10** by solvent. The smaller and polar solvents (acetonitrile, alcohols and water) solvate anions **9** and **10** more effectively than pyrrolidine and may be the reason why rearrangement was preferred in alcohols and acetonitrile. All compounds were characterized through ¹H NMR, ¹³C NMR and HRMS.

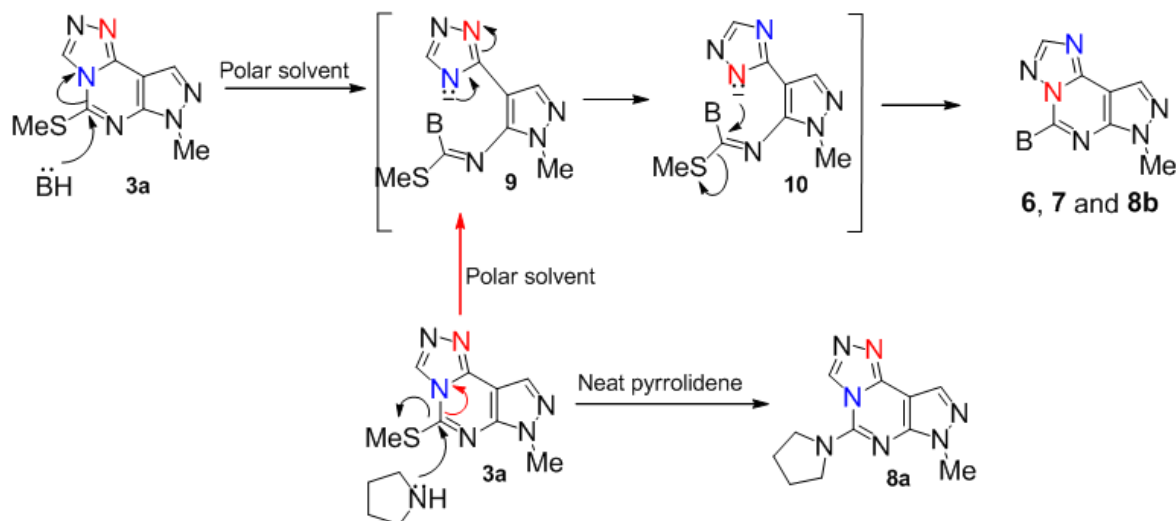


Figure 3. Plausible mechanism for the formation of rearranged product and normal product.

Conclusion

In conclusion, we have presented a facile strategy for the general synthesis of the title compounds **6**, **7** and **8** along with their starting **3** and purine analogue **5**. Such new heterocycles may be useful in pharmacological assays to determine their activities as xanthine oxidase inhibitors and human adenosine antagonists. The intermediate **2c** was utilized in synthesis of 6-methylsulfonyl-1*H*-pyrazolo[3,4-*d*]pyrimidine an important derivative of pyrazolo[3,4-*d*]pyrimidine. Currently, work is in progress to determine the scope and generality of these heterocycles for a better understanding of arene interactions so that they can be compared with corresponding bicyclic pyrazolo[3,4-*d*]pyrimidine analogs for molecular recognition studies and will be reported in due course of time.

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CDRI communication. No. 9010.

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