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Rational synthesis of pyrazolopyrimidines *via* cyclocondensation of ynones obtained from the Sonogashira reaction

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Pyrazolopyrimidines combine the structural and electronic properties of both pyrazole and pyrimidine, imparting unique characteristics that make them valuable in medicinal chemistry and drug discovery. We successfully developed an atom economic protocol for the synthesis of a series of pyrazolo-fused pyrimidines by employing various ynones and 3-aminopyrazole using K_2CO_3 as a base in ethanol. The reactions proceeded under milder conditions, furnishing the desired products in moderate to excellent yields.

Introduction

Heterocyclic molecules are fundamental to many scientific and industrial applications.[1] Understanding and synthesizing heterocyclic compounds continue to be a significant area of research with profound implications in various fields. In particular, pyrazolo-fused pyrimidines display unique properties and a diverse range of biological activities due to the cumulative effect of pyrazole and pyrimidine moieties, making them indispensable in drug development.[2–5] Pyrazolo-fused pyrimidine-based drugs are present in the market, like ocinaplon (**A**) for anxiety, zaleplon (**B**) and indiplon (**E**) as sedatives, presatovir (**C**) as an anti-infective agent and pyrazophos (**D**) as a fungicide (Fig. 1).[6–17] Therefore, the scientific community has put substantial effort into the experimental research and synthesis of these compounds.[18–20] Among the reported methods, protocols using environmentally benign conditions[21,22] are in demand and require future synthesis.

A lot of interest has been shown in the efficient synthesis of these molecules by applying sustainable and environmentally friendly techniques, including atom-economic processes.[23] In addition to adhering to the principles of green chemistry, these approaches have the potential to provide potent anticancer medicines.

Keeping the biological importance of pyrazolo-fused pyrimidines in view, conventional synthetic methods have been developed for their synthesis. Carbonyl compounds and aminopyrazole using Rh and Cu catalysts at 150 °C and 120 °C were employed for the synthesis of pyrazolopyrimidines in 2018 and 2023, respectively (Scheme 1a and c).[24,25] In 2020, Yu and group reported the synthesis of pyrazolopyrimidines in the presence of $FeNi_3$/gold nanoparticles, supported by magnetic ionic gelation under solvent-free conditions (Scheme 1b).[26] Besides, many other reports have involved conventional methods.[27–30] Previously, we also reported a transition-metal-free approach for the chemo-selective synthesis of pyrazolo-fused pyrimidines and their derivatives from acetophenones and aminopyrazole by employing acetic acid as a solvent at 80 °C for 24 h (Scheme 1d).[31] Considering the importance of a greener approach, we attempted to develop a method that uses a greener solvent. In this process, we established a novel, kinetically efficient, transition-metal-free methodology for the synthesis of pyrazolo pyrimidines by employing aminopyrazole with various naphthalenes and thiophenes based on ynones in ethanol.

Results and discussion

Optimization of reaction conditions

We conducted a comprehensive investigation of the reactions between ynone (**2h**) and 3-amino pyrazole (**1**) to establish robust synthetic parameters for the efficient synthesis of pyrazolopyrimidines. Through systematic analysis, we explored the effects of base strength, solvent polarity, reaction temperature and reaction time on reaction efficiency. After careful modulation of

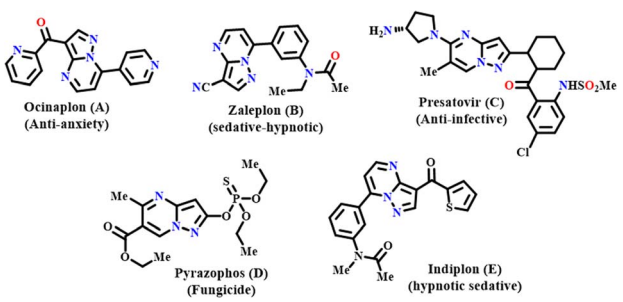

Fig. 1 Pyrazolo-fused pyrimidine-based marketed drugs.

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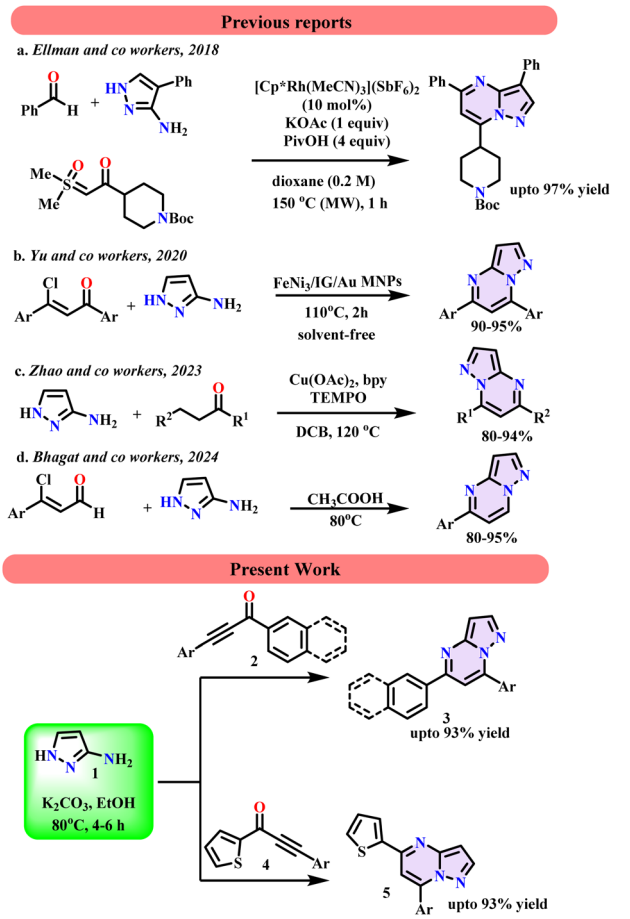


Scheme 1 Previous reports *vs* present work.

these variables, we were successful in identifying the optimal reaction conditions that maximize our yield and minimise ecological footprint. We started with the optimisation of the reaction with ynone (1.0 eq.) and 3-aminopyrazole (**1**, 1.5 eq.) using KOH as a base in DMSO at 100 °C for 12 h (Table 1, entry 1). Contrary to our expectations, the reaction did not proceed to completion, and the desired product was obtained in a low yield of 12%. We further increased the amount of base and obtained an 18% yield (**3h**) (Table 1, entry 2). Re-evaluating, we carried out the reaction in K_2CO_3 in DMSO and DMF for 12 hours, but the anticipated increase in yield was not achieved, as the observed results fell short of our expectations (Table 1, entries 3 and 4). We further investigated the reaction in water at 80 °C for 12 hours (Table 1, entry 5), resulting in a slight increase in the yield of the desired product. Upon further optimising the reaction conditions by changing the solvent to ethanol, we successfully obtained a 56% yield for our desired product (Table 1, entry 6). Continuing our optimisation, by maintaining the reaction temperature at 80 °C, and increasing the amount of K_2CO_3, we successfully obtained 85% yield of our product (Table 1, entry 7). Again, modifying and performing the reaction at room temperature in the same solvent gave a similar yield; however, the reaction took 22 hours to complete (Table 1, entry 8). At 0 °C, no successful result was obtained (Table 1, entry 9).

Table 1 Optimization of reaction conditions[a,b]

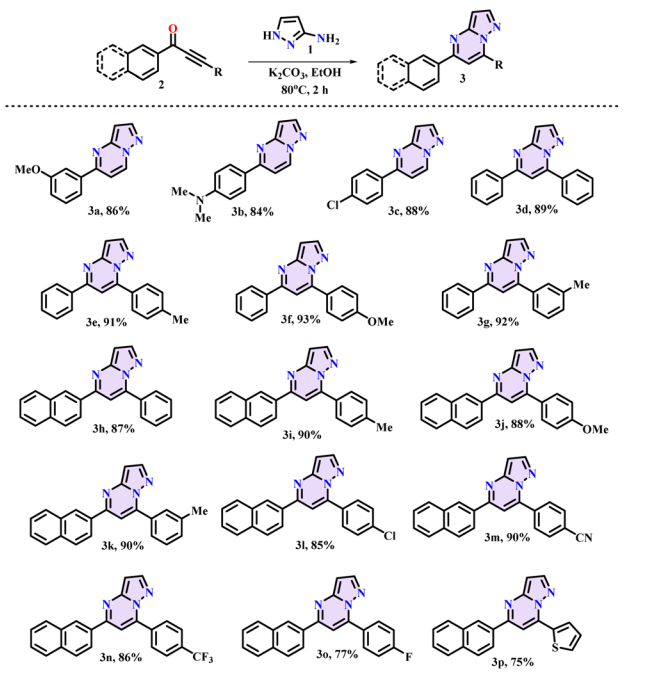
S. no.	Base	Solvent	Temp	Time	Yield
1	KOH (1.0 mmol)	DMSO	100	12	12
2	KOH (2.0 mmol)	DMSO	100	12	18
3	K_2CO_3 (1.0 mmol)	DMSO	100	12	10
4	K_2CO_3 (1.0 mmol)	DMF	100	12	15
5	K_2CO_3 (1.0 mmol)	H_2O	80	12	35
6	K_2CO_3 (1.0 mmol)	EtOH	80	10	57
7	**K_2CO_3(2.0 mmol)**	**EtOH**	**80**	**6**	**85**
8	K_2CO_3 (2.0 mmol)	EtOH	RT	24	68
9	K_2CO_3 (2.0 mmol)	EtOH	0	24	—

[a] Reaction conditions: reactions were carried out using substituted ynones (**2**, 1 eq.) and 3-amino pyrazole (**1**, 1.5 eq.) in an appropriate solvent (2 mL). [b] Isolated yield.

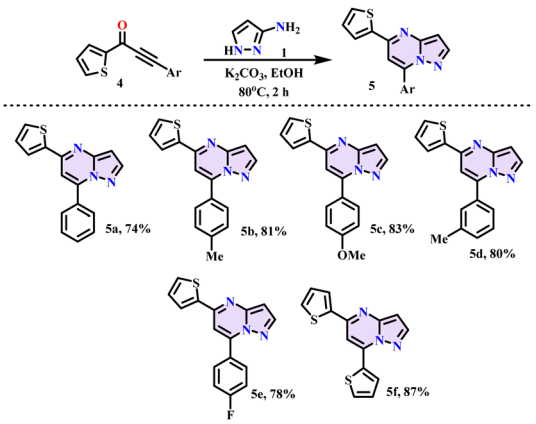
The substrate scope of the reaction was investigated with a wide range of ynones (**2**) and 3-amino pyrazole (**1**) in order to create transition metal-free chemo-selective C–N linkages after determining the ideal conditions (Scheme 2). The desired products were obtained in good-to-excellent yields with great functional group tolerance, such as –F, –Cl, –OMe, $-NMe_2$, $-CF_3$, and CN. Further, the reaction was compatible with thiophene-substituted ynones (**4**) (Scheme 3). We employed the method shown in Scheme 3 to produce equivalent pyrazolo-fused pyrimidines (**5**) in good yields.

Plausible mechanism

After successful analysis of the transition metal-free C–N bond formation process for the synthesis of pyrazolo-fused pyrimidines, a tenable mechanism was put forth (Scheme 4). In this



Scheme 2 Synthesis of benzene-/naphthalene-substituted pyrazolo pyrimidines (**3a–3p**).



Scheme 3 Synthesis of thiophene-substituted pyrazolo pyrimidines (5a–5f).

plausible mechanism, the reaction started with the abstraction of an acidic proton in the presence of a base, which attacked the allylic carbon of the ynone (**2**) to form the allene intermediate (**7**). A similar intermediate was observed by Verma *et al.* in 2012.[32] This intermediate underwent proton transfer, followed by the cyclization reaction (**9**), which led to the final pyrazolo fused pyrimidines (**3**) with the elimination of a water molecule. We synthesised the final products **3(a–p)** and **5(a–f)**, and their structures were confirmed by the ^{1}H and ^{13}C NMR and HRMS spectral data. These results support the assertion that the proposed reaction mechanism proceeds through cyclo-condensation, as shown in Scheme 4.

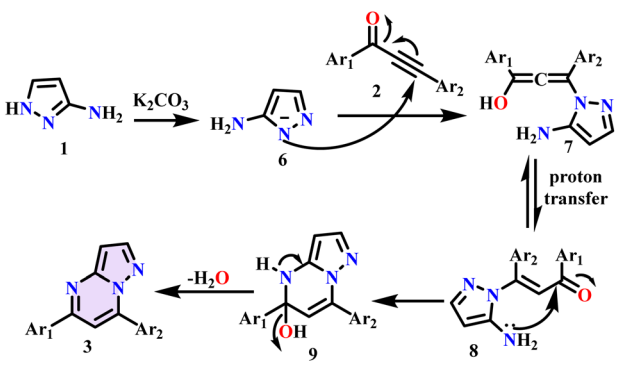
Calculation of green chemistry metrics for the scale-up reaction of product (**3**):

A green chemistry matrix is calculated based on the following parameters:

(1) E-factor or environmental factor.
(2) Atom economy (AE).
(3) Product mass intensity (PMI).
(4) Reaction mass efficiency (RME).

E-factor: E-factor is defined as the ratio of the mass of waste to the mass of the product.

$$\text{E-Factor} = \text{Amount of waste/Amount of product}$$



Scheme 4 Plausible mechanism for the synthesis of pyrazolo pyrimidines.

Amount of reactants: ynone (**1**) = 1.0 mmol and 3-aminopyrazole (**2**) = 1.5 mmol

Total amount of reactants (**1h** + **2**) = (256.30 mg $mmol^{-1}$ × 1.0 mmol) + (83.09 mg $mmol^{-1}$ × 1.5 mmol) = 256.30 mg + 124.64 mg = 380.94 mg = 0.381 g

Amount of product (**3h**) = 0.257 g

Amount of waste = 0.381 g − 0.257 g = 0.124 g

E-factor = 0.124/0.257
= 0.48 (Ideal value of E-factor is considered zero.)

Process mass index (PMI): PMI is defined as the total mass used in a chemical process divided by the mass of the product.

$$\text{PMI} = \Sigma(\text{mass of stoichiometric reactants + solvent})/\text{mass of product (3h)}$$

$$\text{PMI} = (256.30\ \text{mg} \times 1.0) + (83.09\ \text{mg} \times 1.5)/257 = 1.48$$

OR

$$\text{PMI} = \text{E-factor} + 1 = 0.48 + 1 = 1.48$$

Atomic economy (AE): AE of a chemical reaction is a measure of the efficiency of that reaction with regard to how many atoms from the starting materials reside within the product. The ideal value of the AE factor is 100% (*i.e.*, all atoms from the starting materials reside in the product).

$$\text{Atom economy (AE)} = \text{MW of product} \div \Sigma\ (\text{MW of stoichiometric reactants}) \times 100$$

Molecular weight of product (**3h**) = 321.38 g mol^{-1}

Molecular weight of stoichiometric reactants (**1h** + **2**) = (256.30)(1.0) + (83.09)(1.5) = 380.94 g mol^{-1}

Atom economy (AE) = 321.38 × 100/380.94 = 84.4%

Reaction mass efficiency (RME): Reaction mass efficiency is defined as the mass of the product divided by the sum of the total mass of the stoichiometric reactants. The value of the RME varies from 0 to 100%. A larger number of RME is considered better as it is the measure of "cleanness" of the reaction.

$$\text{Reaction mass efficiency} = \text{mass of product}/\Sigma(\text{mass of stoichiometric reactants}) \times 100$$

Mass of product (**3h**) = 0.257 g

Total mass of reactants (**1h** + **2**) = (256.30 mg $mmol^{-1}$ × 1.0 mmol) + (83.09 mg $mmol^{-1}$ × 1.5 mmol) = 256.30 mg + 124.64 mg = 380.94 mg = 0.381 g

RME = (0.257 ÷ 0.381) × 100 = 67.4%. The main text of the article should appear here with headings as appropriate.

Conclusions

Pyrazolo-fused pyrimidine heterocycles have a variety of biological functions and possible therapeutic uses that emphasise their medicinal importance. Ynones obtained from Sonogashira coupling reactions were used to create a new, environmentally friendly, transition-metal-free synthesis technique that ensures atom economy.

Author contributions

Ms. Nikita Goel: writing – review & editing, writing –original draft, visualization, validation, conceptualization, Prof. Sunita Bhagat: visualization, supervision, investigation and Dr Pradeep Kumar and Dr Poonam Kumari: writing – review & editing.

Conflicts of interest

There are no conflicts to declare.

Data availability

Experimental details and spectral data for all new compounds have been included as part of the supplementary information (SI). Supplementary information: ref. 33–36 are cited in the SI. See DOI: https://doi.org/10.1039/d5ra08856a.

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