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REGULAR ARTICLE

Synthesis of 7-arylethyl-5-arylpyrazolo[1,5-*a*]pyrimidines through an aza-Michael addition/nucleophilic addition/1,3-hydrogen transfer cascade

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Abstract. An efficient method for the synthesis of pyrazolo[1,5-*a*]pyrimidines by the tandem reactions of dienones with pyrazole-3-amine through an aza-Michael addition/nucleophilic addition/1,3-hydrogen transfer process in the presence of potassium hydroxide is described. This protocol offers access to 7-arylethyl-5-arylpyrazolo[1,5-*a*]pyrimidines in good to excellent yield. Meanwhile for 4-substituted dienones, different products, 7-arylethylene-5-arylpyrazolo[1,5-*a*]pyrimidines, are given through an aza-Michael addition/nucleophilic addition/oxidation process. A gram-scale reaction has been performed to demonstrate the potency of optimized procedure for the scale-up process.

Keywords. Pyrazole-3-amine; dienone; pyrazolo[1, 5-*a*]pyrimidine; tandem reaction; heterocyclization.

1. Introduction

During the past decade, the synthesis of pyrazolo[1,5-*a*]pyrimidine derivatives and the investigation of their chemical and biological behavior have gained more importance due to pharmaceutical reasons.[1,2] For example, the hypnotic drug Zaleplon (I),[3] the anticancer agent Dinaciclib (II),[4] the fungicide Pyrazophos (III),[5] the hypnotic sedative Indiplon (IV)[6] and the anxiolytic drug Ocinaplon (V)[7] all have this structural motif of pyrazolo[1,5-*a*]pyrimidine (Figure 1). In parallel to medicinal chemistry, discoveries in material sciences have proved that pyrazolo[1,5-*a*]pyrimidines containing an arylazo or heteroarylazo group are useful synthetic intermediates in the dyestuff industry.[8–11] Consequently, synthetic methodologies for novel pyrazolo[1,5-*a*]pyrimidine derivatives are of particular interest to organic and medicinal chemists.

The recently reported methods for the synthesis of pyrazolo[1,5-*a*]pyrimidines include i) gold-acid-co-catalyzed reactions of propargylic hydroperoxides with 3-aminopyrazole;[12] ii) the base induced reactions of 1,3,5-trisubstituted pentane-1,5-diones with substituted pyrazoles;[13] iii) the base catalyzed reactions of chalcones with 3-aminopyrazoles;[14] iv) the reactions of 1,2-allenic ketones with 3-aminopyrazoles;[15] v) the concentrated hydrochloric acid catalyzed condensation of 1,3-diketones with substituted aminopyrazoles;[16] vi) the hydrotalcite catalyzed reactions of enaminones with aminopyrazole derivatives;[17] and vii) the condensation of 2-pyrone with 3-amino-5-arylpyrazoles.[18] However, commercially unavailable reagents, harsh reaction conditions, and regioselectivity concerns restricted their use in regular processes. Therefore, straightforward and more efficient approaches which enable to access these structures in a more efficient manner by means of readily available and highly economical precursors and reagents are quitedesirable.

In this paper, we report an efficient method for the synthesis of 7-arylethyl-5-arylpyrazolo[1,5-*a*]pyrimidines by one-step tandem reactions of commercially available and easily prepared dienones with pyrazole-3-amine through a aza-Michael addition/nucleophilic addition/1,3-hydrogen transfer process in the presence of potassium hydroxide.

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Electronic supplementary material: The online version of this article (doi:10.1007/s12039-017-1365-4) contains supplementary material, which is available to authorized users.

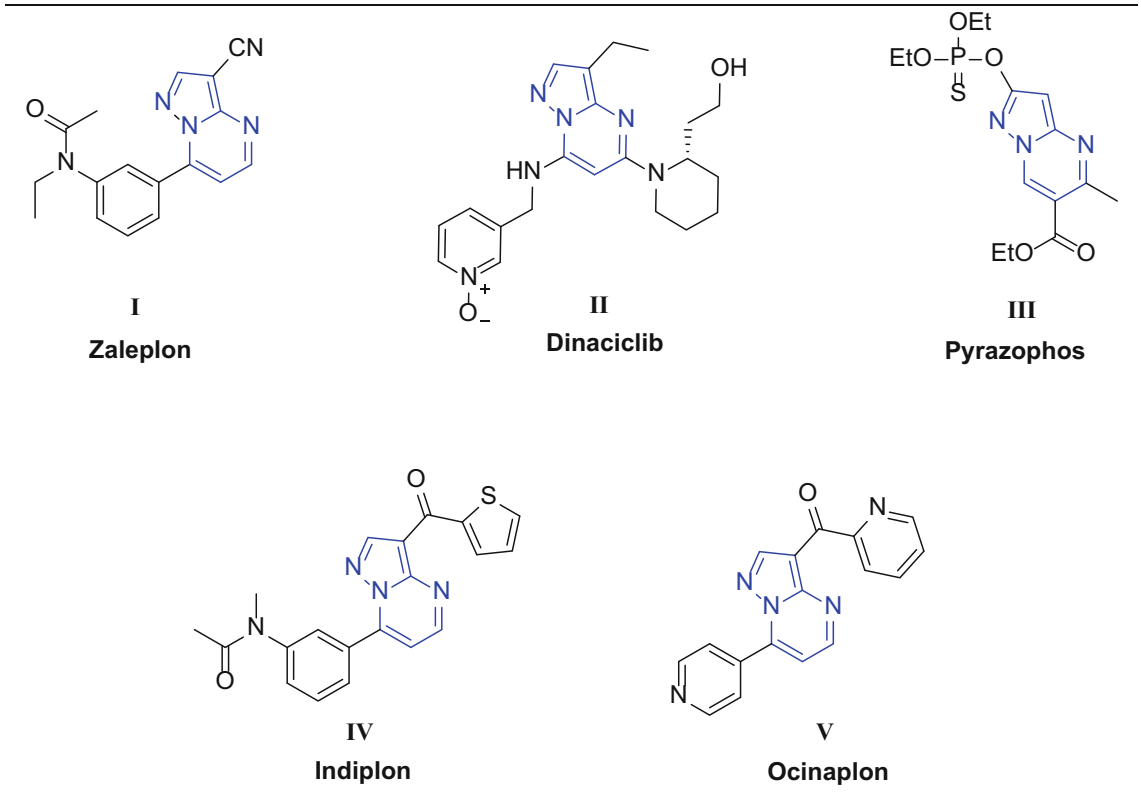


Figure 1. Examples of pyrazolo[1,5-*a*]pyrimidine drugs.

2. Experimental

2.1 *General information*

^{1}H NMR and ^{13}C NMR spectra were obtained with Mercury–600BB instrument using $CDCl_3$ as solvent and Me_4Si as the internal standard. Elemental analyses were performed on a Vario El Elemental Analysis instrument. Melting points were observed in an electrothermal melting point apparatus. Dienones were synthesized according to literature method.[19]

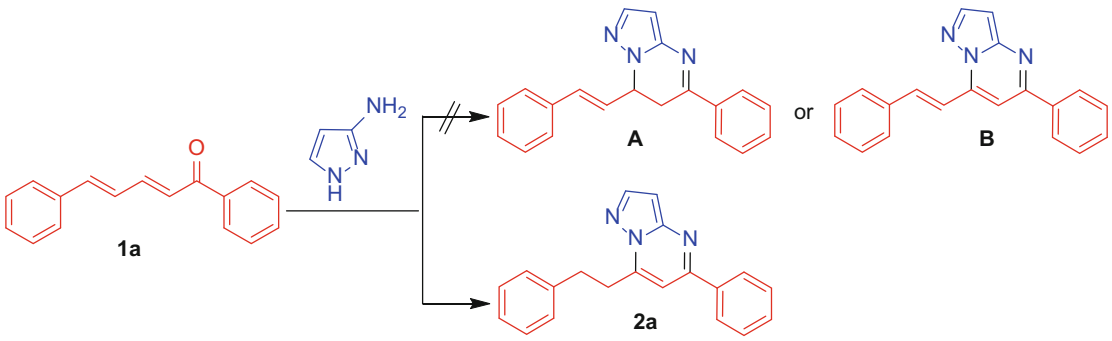
2.2 *General procedure for synthesis of 7-arylethyl-5-arylpyrazolo[1,5-a]pyrimidines* ***(2a–u)*** *and 7-arylethylene-5-arylpyrazolo[1,5-a]pyrimidines* ***(3a-e)***

The mixture of dienone (0.5 mmol), pyrazol-3-amine (0.6 mmol) and potassium hydroxide (0.5 mmol) in *n*-propanol (5 mL) was stirred under air at 100°C for 1 h. The reaction was monitored by TLC. After the completion of the reaction, the mixture was extracted with ethyl acetate (3 × 10 mL), and the combined liquid was washed with saturated brine (3 × 10 mL). The resulting organic phase was dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was isolated by column chromatography using petroleum ether and ethyl acetate (v/v 10:1) as eluent to give pure product. The analytical data for products are given in Supporting Information section.

3. Results and Discussion

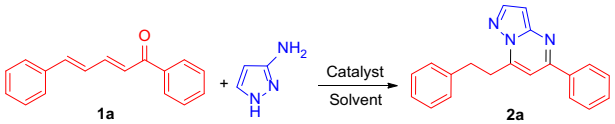
Initially, (2*E*, 4*E*)-1,5-diphenylpenta-2,4-dien-1-one (**1a**) was selected as a model substrate to react with pyrazol-3-amine using *n*-propanol as solvent and potassium hydroxide as a base (Scheme 1). The reaction might take place through 1,4-aza-Michael addition and nucleophilic addition to afford **A** as a final product, or **A** continue to oxidize to **B** as a final product. However, the expected product was not observed. Instead, an unexpected product, 7-phenethyl-5-phenylpyrazolo[1,5-*a*] pyrimidine (**2a**), was isolated, which was confirmed by ^{1}H NMR and ^{13}C NMR spectra. This result indicated that 1,3-hydrogen transfer also occurred for the reaction of **1a** and pyrazol-3-amine in addition to 1,4-aza-Michael addition and nucleophilic addition. The possible reason is that compared to structure **A**, the product **2a** has more stable aromatic fused heterocycle. This implied that the driving force for 1,3-hydrogen transfer is to form more stable structure.

In order to optimize the reaction conditions, the different solvents and bases were screened (Table 1). When various solvents were tested, it was found that the reaction could not proceed in toluene and xylene (Table 1, entries 1, 2). Moderate yields of **2a** were obtained in DMF, DMSO, 1,4-dioxane, EtOH and *n*-BuOH (Table 1, entries 3–7). However, the best yield



Scheme 1. The reaction of **1a** with pyrazol-3-amine.

Table 1. Condition optimization for reaction of **1a** with pyrazol-3-amine.[a]



Entry	Base	Solvent	Temperature (°C)	Yield (%)[b]
1	KOH	Xylene	110	NR[c]
2	KOH	Toluene	110	NR[c]
3	KOH	DMF	110	59
4	KOH	DMSO	110	20
5	KOH	1,4-Dioxane	100	55
6	KOH	EtOH	80	35
7	KOH	*n*-BuOH	110	78
8	KOH	*n*-PrOH	100	85
9	NaOH	*n*-PrOH	100	80
10	K_2CO_3	*n*-PrOH	100	40
11	Cs_2CO_3	*n*-PrOH	100	50
12	$NaHCO_3$	*n*-PrOH	100	33
13	DBU	*n*-PrOH	100	NR[c]
14	DABCO	*n*-PrOH	100	NR[c]
15	DMAP	*n*-PrOH	100	NR[c]
16	Et_3N	*n*-PrOH	100	NR[c]

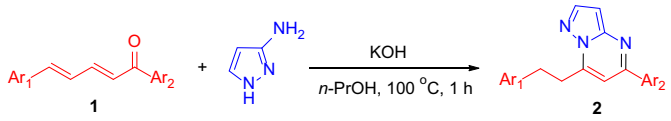
[a]Reaction conditions: **1a** (0.5 mmol), pyrazol-3-amine (0.6 mmol) and base (0.5 mmol) in solvent (5 mL) at appropriate temperature for 1 h.
[b]Isolated yields.
[c]No reaction.

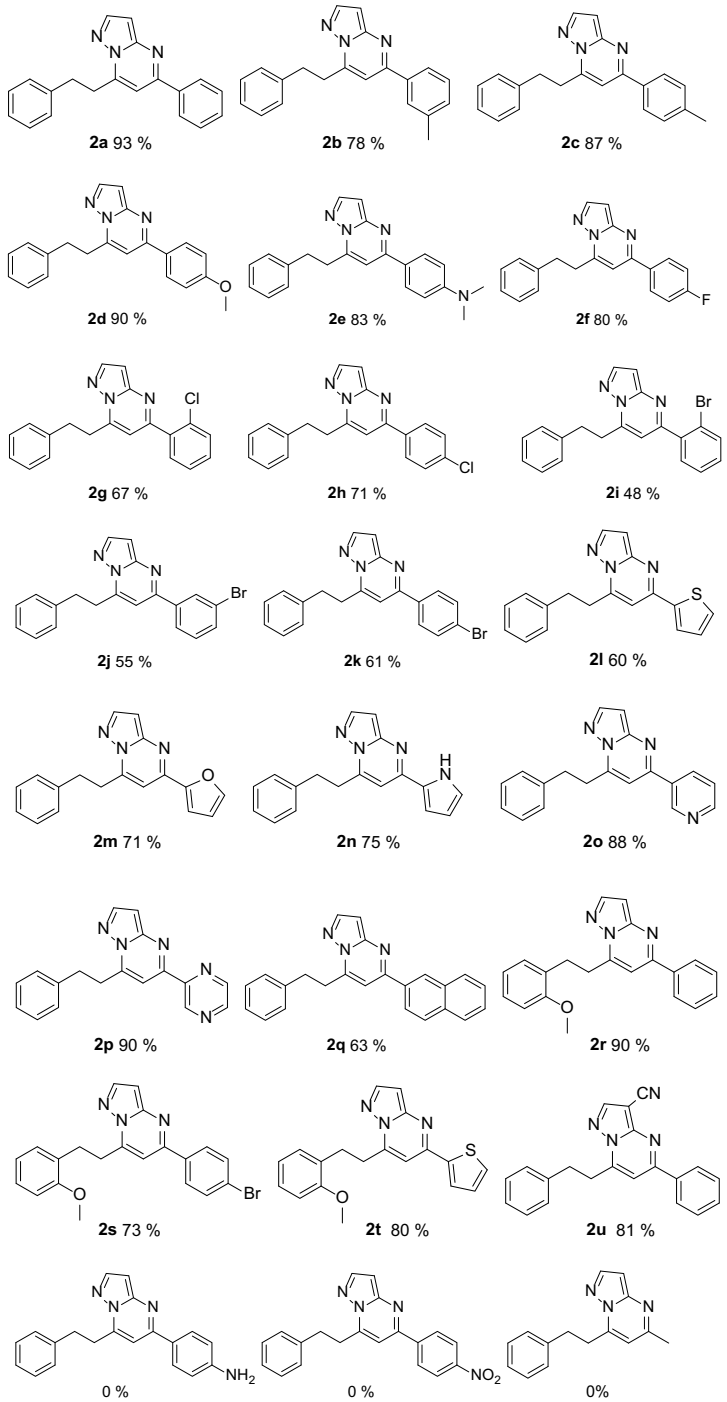
was obtained by using *n*-PrOH as solvent (Table 1, entry 8).

In addition, bases also played an important role in the reaction. Some tested inorganic bases, such as NaOH, K_2CO_3, Cs_2CO_3 and $NaHCO_3$, had a certain effect on the reaction (Table 1, entries 9–12). Organic bases, such as DBU, DABCO, DMAP and Et_3N could not promote the reaction (Table 1, entries 13–16). The highest yield of **2a** was obtained by using KOH as a base (Table 1, entry 8).

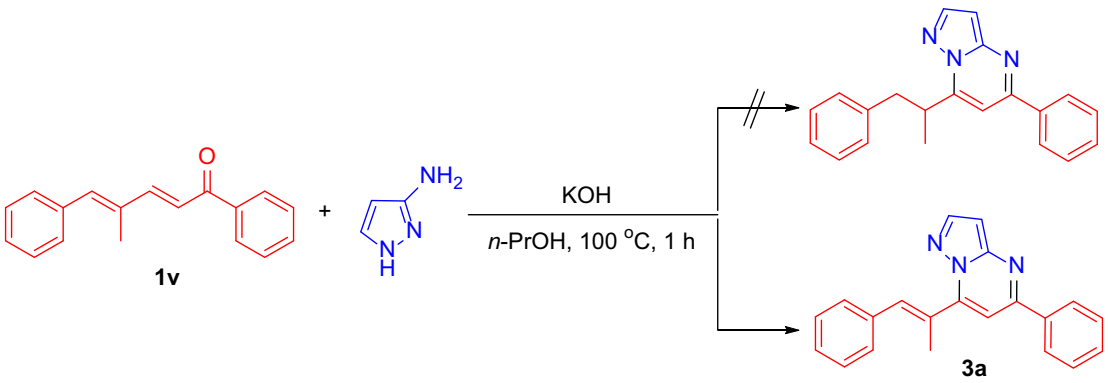
With the optimal conditions in hand, we turned our focus to unearth the generality of the method to access various 7-arylethyl-5-arylpyrazolo[1,5-*a*]pyrimidines, and the results are summarized in Table 2. It was found that the reactions could tolerate a wide range of functional groups, and produce the corresponding products in good to high yield. Dienones bearing electron-donating groups (Me, MeO and NMe_2) on aromatic rings of Ar_1 and Ar_2 gave the corresponding products in higher yield (Table 2, **2b**–**2e**, **2r**–**2t**). In contrast, dienones bearing electron-withdrawing groups (F, Cl and Br) on aromatic rings of Ar_2 gave slightly lower yield (Table 2, **2f**–**2k**). In addition, dienones containing heterocyclyls, such

Table 2. Substrate scope for the tandem synthesis of 7-arylethyl-5-arylpyrazolo[1,5-*a*]pyrimidines.



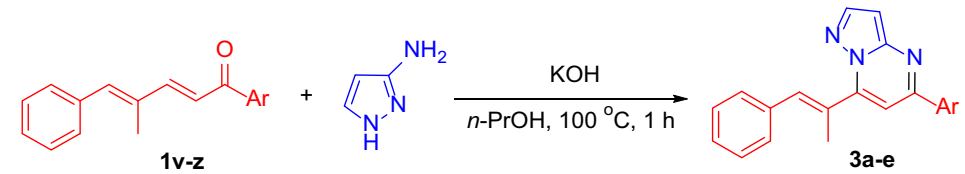


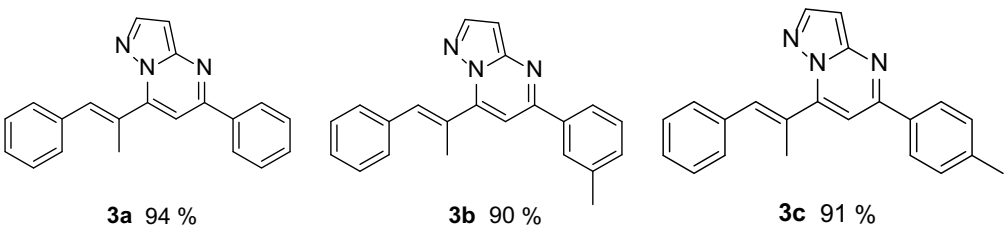
Reaction conditions: dienones **1a–u** (0.5 mmol), pyrazol-3-amine (0.6 mmol) and potassium hydroxide (0.5 mmol) in *n*-propanol (5 mL) at 100°C for 1 h.



Scheme 2. The reaction of 4-Me substituted dienone **1v** with pyrazol-3-amine.

Table 3. The substrate scope for the synthesis of 7-arylethylene-5-arylpyrazolo[1,5-*a*]pyrimidines.

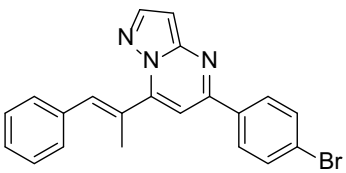




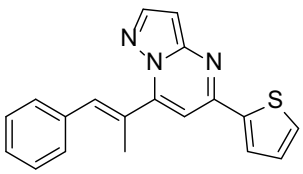
3a 94 %

3b 90 %

3c 91 %



3d 83 %

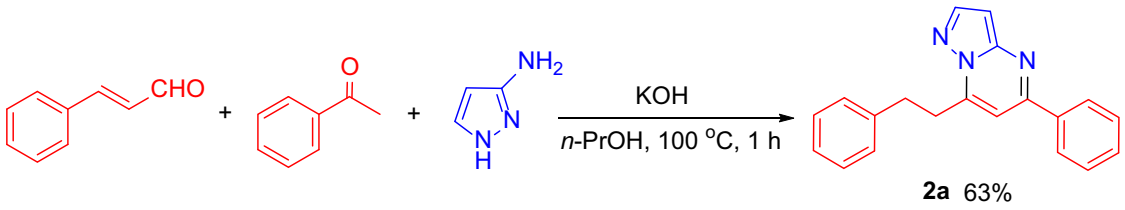


3e 86 %

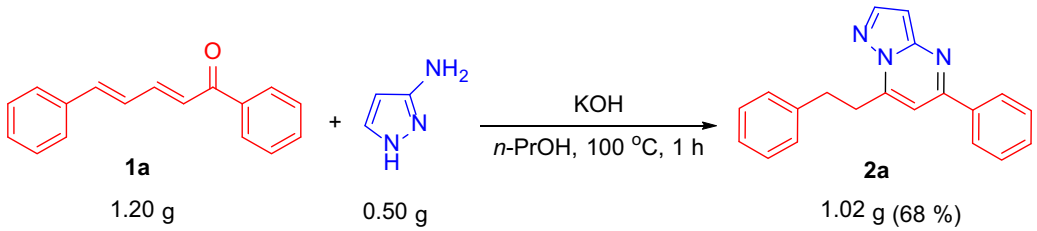
Reaction conditions: dienone **1v–z** (0.5 mmol), pyrazol-3-amine (0.6 mmol) and potassium hydroxide (0.5 mmol) in *n*-propanol (5 mL) at 100°C for 1 h.

as thienyl, furanyl, pyrrolyl, pyridinyl and pyrazinyl, could transform into the desired products in good yield (Table 2, **2l–2p**,**2t**). Unfortunately, the reactions for dienones bearing nitro and amino groups on aromatic rings of Ar_2 were not successful. The tested aliphatic dienones did not give the corresponding product. The reactions of dienone with substituted pyrazol-3-amine, such as 4-cyanopyrazol-3-amine, could also give the corresponding heterocycle in high yield (Table 2, **2u**).

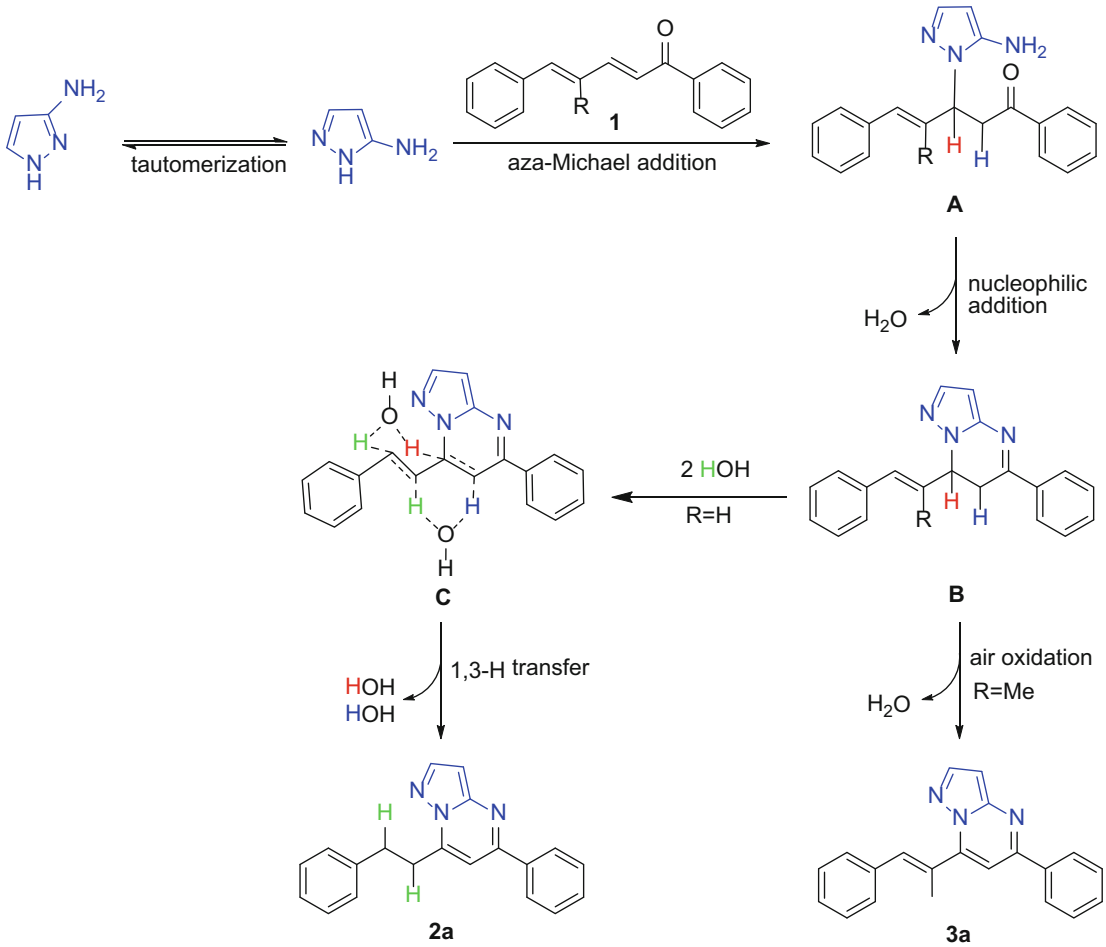
It was noteworthy to mention that when 4-substituted dienone, such as 4-Me substituted dienone **1v**, was used as a substrate, the reaction could not give the similar 7-phenylethyl product, instead a 7-phenylethylene product **3a** was efficiently afforded in high yield under the standard conditions, and no other by-products were observed (Scheme 2). This result indicated that the reaction might undergo a different air oxidation process in addition to 1,4-aza-Michael addition and nucleophilic addition compared with analogous reaction of



Scheme 3. Synthesis of **2a** by one-pot three-component method.



Scheme 4. Practical synthesis of **2a** on gram scale.



Scheme 5. The proposed mechanism for **2a** and **3a**.

1a. The possible reason is that the existence of 4-Me in dienone **1v** hindered the 1,3-hydrogen transfer. And another conjugate fused heterocycle structure was produced by dehydrogenation oxidation in the presence of air.

This reaction could also extend to other similar 4-Me substituted dienones bearing different substituents (such as Me, Br) on aromatic rings (Table 3, **3b–d**) and heteroaryl (such as thienyl) (Table 3, **3e**) to give the corresponding products in high yield.

The synthesis of **2a** could also be conducted through a one-pot three-component reaction of cinnamaldehyde, acetophenone and pyrazol-3-amine in 63% yield by the standard conditions (Scheme 3).

With the success over generality of the protocol, the reaction of dienone **1a** with pyrazol-3-amine was also performed on gram scale. The reaction of 1.20 g of **1a** with 0.50 g of pyrazol-3-amine in the presence of 0.28 g of potassium hydroxide in *n*-propanol (15 mL) was performed under the optimized condition to give 1.02 g of **2a** in 68% isolated yield. This success of gram scale reaction further showed the potency of optimized condition for the bulk processes (Scheme 4).

A plausible mechanism is proposed for the synthesis of **2a** and **3a** (Scheme 5). Pyrazol-3-amine first tautomerizes to pyrazol-5-amine, which attacks the dienone **1** through 1,4-aza-Michael addition to give intermediate **A**. Then the amino group of **A** nucleophilically attacks the intramolecular carbonyl group, followed by dehydration to afford intermediate **B**. The intermediate **B** (R=H) with assistance of two moles of water can afford intermediate **C**, which can easily undergo loss of two moles of water to achieve 1,3-hydrogen transfer to give **2a** as a final product. Meanwhile intermediate **B** (R=Me) can also undergo dehydrogenation oxidation in the presence of air by loss of water to afford **3a** as a final product.

4. Conclusions

In conclusion, we have developed a simple and effective method for the synthesis of 7-arylethyl-5-arylpyrazolo [1,5-*a*]pyrimidines through aza-Michael addition/nucleophilic addition/1,3-hydrogen transfer tandem reactions of dienones with pyrazol-3-amine in the presence of potassium hydroxide. For the 4-substituted dienones, different products, 7-arylethylene-5-arylpyrazolo[1,5-*a*]pyrimidines, were obtained through aza-Michael addition/nucleophilic addition/oxidation process. Mild reaction conditions, shorter reaction time, high yield, good functional group tolerance and simple work-up procedure are some of the salient features of this protocol. A gram-scale reaction has been attempted to illustrate the potency of reported procedure towards the bulk synthesis. This method will be an important alternative to multifunctional intermediates including pyrazolo[1,5-*a*]pyrimidine, aryls and alkenyl, and will possibly find potential applications in medicinal chemistry and material chemistry.

Supplementary Information (SI)

Full set of characterization data (^{1}H and ^{13}C NMR spectra) and Figures S1-S52 are available at www.ias.ac.in/chemsci.

Acknowledgements

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