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Synthesis of Novel Imidazo[1,2-*a*]pyrimidin-5(1*H*)-one Derivatives by Intramolecular Cycloisomerization of 2-Amino-3-alkynylpyrimidin-4(3*H*)-one in the Presence of Aqueous Base

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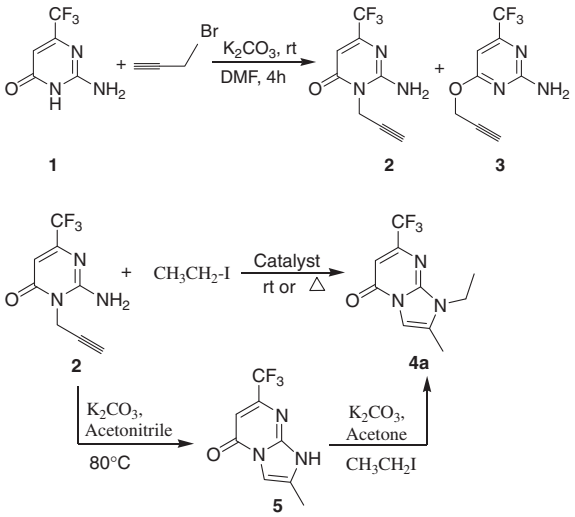
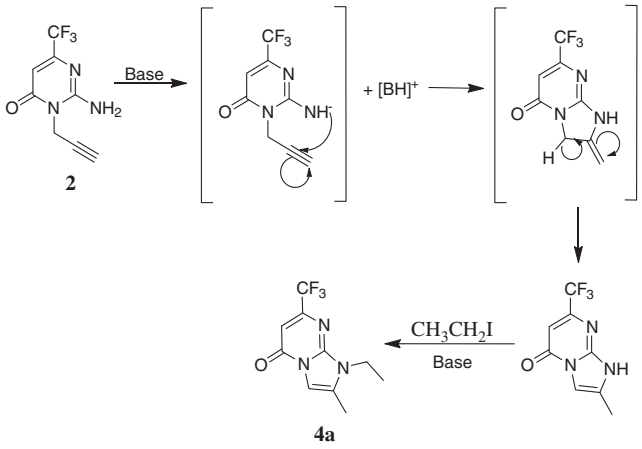
An efficient strategy has been developed for the synthesis of novel imidazo[1,2-*a*]pyrimidin-5(1*H*)-one derivatives **4** from 2-amino-3-alkynylpyrimidin-4(3*H*)-one **2** and alkyl halides in a single step by intramolecular cycloisomerization followed by N-alkylation in the presence of aqueous base.

The imidazo[1,2-*a*]pyrimidine nuclei are present in many biologically active compounds, and their derivatives are found to possess anxiolytic,[1] cardiovascular,[2] analgesic,[3] antihypertensive,[4] and neuroleptic[5,6] activities. The structure of the imidazo[1,2-*a*]pyrimidine is related to the purine ring system and possesses anti-inflammatory,[7] as well as insecticidal, acaricidal, and nematocidal activities.[8] Because of a wide range of activities, several methods are available for the preparation of imidazo[1,2-*a*]pyrimidine derivatives by fusion of a pyrimidine ring over imidazole and vice versa. Thus, pyrimidine[9–15] earlier accomplished by the reaction of 1,3-bifunctional compounds with 2-aminoimidazoles as well as imidazoles[16] was prepared by the reaction of 1,2-bifunctional compounds with 2-aminopyrimidine. Further, intramolecular addition of amine to alkynes is a challenging and highly desirable transformation which can be mediated and catalysed by Ru,[17–19] Ag,[20] and Au[21] metal complexes. Recently, imidazo[1,2-*a*]pyrimidine derivatives[22] are also prepared by Pd/C-catalyzed heterocyclization starting from 2-aminopyrimidine. Compounds having fluorine[23] or a trifluoromethyl[24,25] group at a specified position were found to influence dramatically change in reactivity and the properties of molecule in terms of lipid solubility, oxidative thermal stability, and oral bioavailability. Therefore, the trend is driving more toward fluorinated molecules. In view of the importance of imidazo[1,2-*a*]pyrimidine nuclei and trifluoromethyl group, we have designed and accomplished a series of novel imidazo-[1,2-*a*]pyrimidin-5(1*H*)-one derivatives in a single step by intramolecular cycloisomerization in the presence of aqueous base. The method is simple, operated under mild conditions and provides high yield.

The 2-amino-6-trifluoromethyl-3(*H*)-pyrimidin-4-one[26] (**1**) was reacted with 2-propynyl(propargyl) bromide in the presence of base resulting in the formation of two regioisomers i.e., N-propargylated compound **2**[27] (polar) in 80% and O-propargylated product **3**[27] (nonpolar) in 10%. Both the regioisomers were separated based on their difference in polarity. Compound **2** was further reacted with ethyl iodide in the presence of different bases in various solvents at different temperatures, and imidazo-[1,2-*a*]pyrimidin-5(1*H*)-one **4a** was obtained. In order to confirm the reaction sequence, compound **2** was initially cyclized in the presence of K_2CO_3 as a base and acetonitrile as solvent to form imidazo[1,2-*a*]pyrimidine **5**. Compound **5** was further alkylated using alkyl halide to obtain compound **4a**. Out of all the conditions used, reaction temperature 50 °C, reaction time five



Scheme 1. Reaction of 2-amino-6-trifluoromethyl-3(*H*)-pyrimidin-4-one (**1**) with propargyl bromide and reaction of 2-amino-3-(2-propynyl)-6-trifluoromethyl-3*H*-pyrimidin-4-one (**2**) with ethyl iodide.



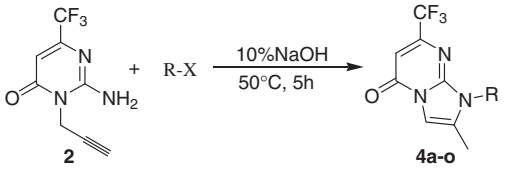
Scheme 2. Mechanistic pathway for the conversion of **2** to **4a**.

hours, and aqueous sodium hydroxide was considered the best medium to give 96% yield. The mechanistic path of the reaction was presumed to be an abstraction of proton from amine by base, and intramolecular cycloisomerization of amine onto alkyne followed by N-alkylation to obtain product **4a**. The detailed reactions outlined in Scheme 1, mechanism in Scheme 2, and products formed in each case are tabulated in Table 1.

The optimized reaction protocol was extended to the reaction of compound **2** with diverse alkyl halides using 10%

Table 1. Preparation of compound **4a** in different solvents and bases

Entry	Solvent	Catalyst	Temp /°C	Time /h	Yield /%
1	H_2O	K_2CO_3	60	24	—
2	H_2O	NaOH	RT	24	70
3	H_2O	NaOH	50	5	96
4	H_2O	Et_3N	60	6	93
5	H_2O	Piperidine	60	5	91
6	DMF	NaOH	80	6	86
7	DMF	K_2CO_3	80	7	90
8	THF	K_2CO_3	70	24	—
9	THF	Et_3N	70	24	—
10	CH_3CN	K_2CO_3	RT	24	30
11	CH_3CN	Et_3N	RT	24	—
12	CH_3CN	K_2CO_3	90	6	89
13	EtOH	K_2CO_3	80	24	—
14	EtOH	Et_3N	80	24	—
15	MeOH	K_2CO_3	70	24	—



Scheme 3. Preparation of substituted imidazo[1,2-*a*]pyrimidin-5(1*H*)-one derivatives.

Table 2. Preparation of compounds **4a**–**4o**[a]

S.No	Product	R	Yield[b] /%	Mp /°C
1	**4a**	CH_3CH_2–	96	90–92
2	**4b**	$CH_3(CH_2)_2CH_3$–	89	65–67
3	**4c**	$CH_3(CH_2)_6CH_3$–	92	72–74
4	**4d**	$CH_3(CH_2)_8CH_3$–	85	77–79
5	**4e**	*n*-$C_{10}H_4F_{17}$–	89	130–132
6	**4f**	CH_2=CH–CH_2–	87	76–78
7	**4g**	C_3H_3–	94	83–85
8	**4h**	$CH_3C(O)CH_2$–	84	162–164
9	**4i**	$C_6H_5C(O)CH_2$–	88	181–183
10	**4j**	4-$ClC_6H_4C(O)CH_2$–	96	202–204
11	**4k**	4-$FC_6H_4C(O)CH_2$–	91	170–172
12	**4l**	4-$CF_3C_6H_4C(O)CH_2$–	85	159–161
13	**4m**	$C_6H_5CH_2$–	92	91–93
14	**4n**	4-$FC_6H_4CH_2$–	89	85–87
15	**4o**	4-$ClC_6H_4CH_2$–	95	100–102

[a]All the reactions were carried out using 10% NaOH, 1 equiv of **2** and 1.1 equiv of alkyl halide at 50 °C. [b]Isolated yields.

NaOH as catalyst at 50 °C and provided respective products **4** in high yield. The general reaction is drawn in Scheme 3 and products are tabulated in Table 2.

In conclusion, a straightforward reaction has been developed for the synthesis of a series of novel imidazo[1,2-*a*]-pyrimidine derivatives in a single step and is applicable to the synthesis of diverse substituted imidazo[1,2-*a*]pyrimidine derivatives.[28]

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