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Ionic liquid promoted synthesis of heterocycle-fused pyrimidine-2,4(1*H*,3*H*)-diones utilising CO_2

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ABSTRACT

An efficient ionic liquid system was developed for the preparation of various heterocycle-fused pyrimidine-2, 4(1*H*,3*H*)-diones in moderate to excellent yields (52–95%). It was found that [$HDBN^+$][TFE^-], a simple and easily prepared ionic liquid, could act as both the solvent and reaction promoter, and that the reactions could be efficiently carried out at atmospheric pressures of CO_2.

Introduction

Heterocycle-fused pyrimidine-2,4(1*H*,3*H*)-diones are useful synthetic materials in heterocyclic chemistry, and their derivatives have drawn the attention of chemists and medicinal chemists due to their various biological activities.[1] 5,6-Fused pyrimidines such as pyrido[3,2-*d*]pyrimidine (**I**), thieno[2,3-*d*]pyrimidine (**II**), pyrrolo[2,3-*d*]pyrimidine (**III**), and pteridine (**IV**), are examples of such *N*-heterocycles which can be used as inhibitors or antagonists (Fig. 1).[2] Therefore, the importance of this class of heterocycle has continued to inspire the pursuit of their general and efficient syntheses. Typically, these compounds are prepared by construction of the heterocyclic cores *via* classical methods using harsh conditions, such as the reaction of heterocyclic substrates with urea,[3] chlorosulfonyl isocyanate,[4] potassium cyanate,[5] or phosgene.[6] However, these synthetic routes possess disadvantages such as requiring toxic reagents and multistep procedures, as well as having a negative environmental impact.

In recent decades, the utilization of CO_2 in organic synthesis as an abundant, inexpensive, green and renewable C1 resource has received extensive attention,[7] for example, the reaction of CO_2 and 2-aminobenzonitrile to yield quinazoline-2,4(1*H*,3*H*)-dione.[8] This process represents an atom-economical route to synthesise quinazoline-2,4(1*H*,3*H*)-diones, and various types of catalysts have been investigated to promote these reactions, such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU),[9] 1-butyl-3-methylimidazolium hydroxide,[10] MgO-ZrO_2,[11] Cs_2CO_3,[12] and $TBA_2[WO_4]$.[13] Recently, Han and co-workers described a convenient synthesis of quinazoline-2,4(1*H*,3*H*)-diones from 2-aminobenzonitriles *via* the chemical fixation of carbon dioxide using 1-butyl-3-methylimidazolium acetate ([$Bmim^+$][Ac^-]) as the solvent and promoter.[14] Further-

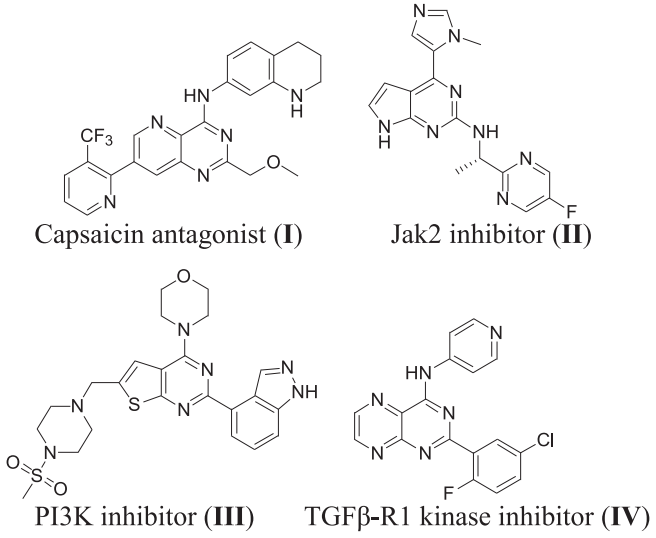

Fig. 1. Selected pharmaceutically relevant 5,6-fused pyrimidines.

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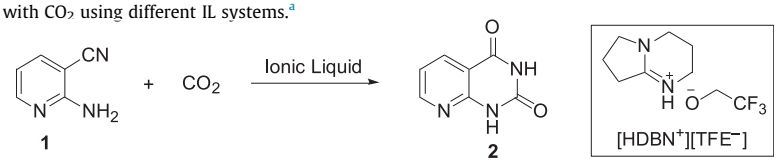
more, Liu and co-workers reported a similar synthesis of quinazoline-2,4(1*H*,3*H*)-diones using [HDBU$^+$][TFE$^-$] as the promoter and solvent.[15] These studies demonstrated that task-specific ionic liquids (ILs) can display superior performance for CO_2 capture and conversion through careful design and choice of the component ions to endow them with unique properties.

Until now, there have been few literature reports regarding the green synthesis of heterocycle-fused pyrimidine-2,4(1*H*,3*H*)-

Table 1
Reaction of 2-amino-nicotinonitrile **1** with CO_2 using different IL systems.[a]



Entry	Ionic liquid	Time [h]	Yield **2** [%][b]
1	–	–	–
2	[HDBU$^+$][TFE$^-$]	3	35
3	[HDBU$^+$][TFE$^-$]	9	90
4	[HDBN$^+$][TFE$^-$]	3	95
5	[HBmim$^+$][Ac$^-$]	9	42
6	[HDBU$^+$][Ac$^-$]	9	–
7[c]	Ionic Liquids [d]	9	–

[a] Reagents and conditions: 2-amino-nicotinonitrile **1** (1 mmol), ionic liquid (6 mmol), CO_2 (balloon), 60 °C.
[b] Isolated yield.
[c] Room temperature.
[d] [HDBN$^+$][TFE$^-$], [HDBU$^+$][TFE$^-$] and [HBmim$^+$][Ac$^-$] were individually used in this reaction.

Table 2
Synthesis of various six-membered ring fused pyrimidine-2,4(1*H*,3*H*)-diones.[a]

Entry	Substrate	T [°C]	Time [h]	Product	Isolated yield **4** [%]
1	**3a**	60	3	**4a**	92
2	**3b**	60	3	**4b**	89
3	**3c**	90	20	**4c**	86
4	**3d**	90	48	**4d**	80
5	**3e**	90	48	**4e**	85
6	**3f**	90	96	**4f**	52

[a] Reagents and conditions: substrate **3** (1 mmol), ionic liquid (6 mmol), CO_2 (balloon).