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COMMUNICATION

Acid- and metal-free synthesis of annulated pyrroles in deep eutectic solvent

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Abstract: An environmentally benign, one-pot, three component synthesis of annulated pyrroles by coupling free sugars with enamines, generated in situ from aryl amines and 1,3-diketones, has been achieved by using deep eutectic solvent (DES). The reaction conditions are mild and do not require additional Bronsted or Lewis acid catalyst.

Introduction

Deep eutectic solvents (DES) have attracted considerable attention as green alternatives to conventional solvents. These not only reduce the burden of disposal of organic solvents but also enhance the rate of many organic reactions. In addition to advantages such as chemical stability and low vapour pressure,[1] deep eutectic solvents are diverse, inexpensive, readily available and have emerged as alternatives to organic solvents.[2–4]

Multi-component reactions (MCRs) in view of their ability to construct complex molecules have become a widely explored area. MCRs are faster and more efficient than classical reactions, since reactions are completed by mere mixing of compounds in one vessel without isolating any intermediates. Additional benefits include readily available starting materials, operational simplicity and ease of automation.[5] The combination of MCR with DES is therefore one of the most suitable strategies for developing libraries of useful scaffolds.[6]

Substituted pyrroles occur in bioactive molecules[7] and also in a wide range of natural products.[8] They also find broad applications in supramolecular chemistry and material science.[9] Hence, several useful strategies have been developed for the construction of the pyrrole moiety.[10] Thus, the development of streamlined methods for their synthesis starting from easily available materials is desirable. Glycosylation of heterocyclic compounds is also a field of increasing interest, in view of various guanidine derived glycosides showing anti-inflammatory and anti-HIV activity.[11] To the best of our knowledge, only two reports[12] for the synthesis of sugar annulated pyrrole derivatives are available. The main disadvantages of these methods are the cost of catalyst,[12a] time required for reaction completion and yield obtained.[12b] Hence, the development of a more practical and economical method for the synthesis of annulated pyrroles is of interest.

In this paper, we disclose a one-pot synthesis of optically pure annulated pyrroles via the cyclization of enamines with free sugars by Knoevenagel condensation under acid- and solvent-free conditions in presence of DES made from choline chloride and urea (see Scheme).

Scheme

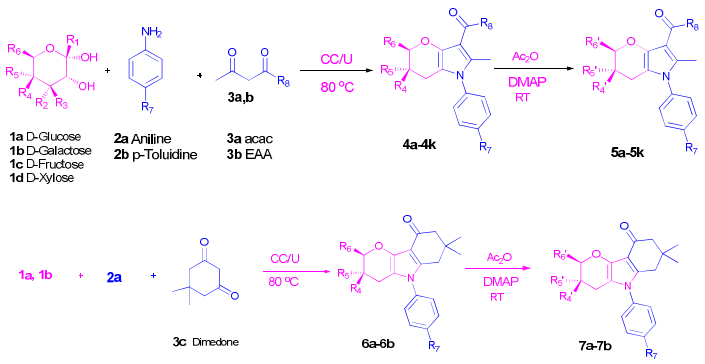

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Table 1 Synthesis of annulated pyrroles in choline chloride: urea (CC/U)

Entry	Sugar	Aryl amine	1,3-dione	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	$R_{4'}$	$R_{5'}$	$R_{6'}$	Acylated product	Time (min)	Yield (%)
1	1a	2a	3a	H	OH	H	H	OH	CH_2OH	H	CH_3	H	OAc	CH_2OAc	5a	30	94
2			3b								OEt				5b	30	92
3			3c								-				7a	45	84
4		2b	3a							CH_3	CH_3				5c	30	92
5			3b								OEt				5d	30	90
6	1b	2a	3a	H	OH	H	OH	H	CH_2OH	H	CH_3	OAc	H	CH_2OAc	5e	30	94
7			3b								OEt				5f	40	92
8			3c								-				7b	45	84
9		2b	3a							CH_3	CH_3				5g	30	90
10			3b								OEt				5h	35	92
11	1c	2a	3a	CH_2OH	H	OH	H	OH	H	H	CH_3	H	OAc	H	5i	45	84
12		2b	3b							CH_3	OEt				5j	45	85
13	1d	2a	3a	H	H	OH	H	OH	H	H	CH_3	H	OAc	H	5k	30	94

5a-5k: Yield after acetylation followed by column chromatography
7a-7b: Reaction of **1a**, **1b** and **2a** with dimedone **3c**

Results and discussion

Initially we attempted the reaction of D-glucose (**1a**) with aniline (**2a**) and acetylacetone (**3a**) in presence of DES at room temperature. However, TLC analysis did not indicate formation of any product. When the reaction was carried out at 80 ^oC for 30 min, we were able to isolate (**4a**) which was identified based on ^1H NMR data of its acetylated derivative (**5a**) (entry 1 in Table 1). When we carried out the reaction at 100 ^oC we observed the formation of several polar side products along with traces of (**4a**)**.** Similar results were obtained when we used DES prepared from choline chloride : malonic acid, choline chloride : ethylene glycol, choline chloride : oxalic acid and choline chloride : TsOH (entries 2-5 Table 2). Further reactions were carried out with DES prepared from choline chloride : urea as it is the least expensive option.

Table 2 Optimization of catalyst in reaction of (**1a**) and (**2a**) with (**3a**)

Entry	Catalyst	Time (h)	Temperature (^oC)	Yield (%)
1	ChCl : Urea	8.0	RT	Traces
		4.0	50	42
		0.5	80	94
		2.0	100	68
2	ChCl : Ethylene glycol	8.0	RT	Traces
		4.0	50	36
		0.8	80	90
		2.0	100	65
3	ChCl : Malonic acid	8.0	RT	Traces
		4.0	50	42
		0.5	80	92
		2.0	100	67
4	ChCl : Oxalic acid	8.0	RT	Traces
		4.0	50	41
		0.5	80	90
		2.0	100	67
5	ChCl : TsOH	8.0	RT	Traces
		4.0	50	40
		0.5	80	93
		2.0	100	66

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In order to evaluate the scope of this protocol we studied the reaction of D-glucose, D-galactose, D-fructose and D-xylose with aniline and p-toluidine and 1,3-dicarbonyl compounds such as acetylacetone (**3a**), ethyl acetoacetate (**3b**) and dimedone (**3c**). In general, all reactions were clean and the corresponding annulated pyrroles, characterized by conversion into di-*O*-acetyl derivatives, were obtained in short reaction times in moderate to high yield (see Table 1). D-Glucose (**1a**) on reaction with aniline (**2a**) and acetylacetone (**3a**) in the presence of DES at 80 °C for 30 min rapidly produced annulated pyrrole derivative (**4a**) in 94% yield. Reaction with p-toluidine (**2b**) resulted in the formation of annulated pyrrole (**4c**) in 93% yield (entries 4 in Table 1). Use of a cyclic 1,3-diketone such as dimedone (**3c**) with D-glucose (**1a**) and aniline (**2a**) afforded annulated pyrroles (**6a**) and (**6b**) in lesser yield (84-88%) (entry 3 and 8 in Table 1). D-Galactose (**1b**) and D-fructose (**1c**) on reaction with anilines (**2a**, **2b**) and 1,3-dicarbonyl compounds (**3a**, **3b**, **3c**) under the same reaction condition afforded the corresponding annulated pyrroles in good yield (entries 6-12 in Table 1). A pentose such as xylose on reaction with aniline (**2a**) and acetylacetone (**3a**) afforded the corresponding annulated pyrrole (**4k**) in good yield (94%, entry 13 in Table 1). In all cases, only a single product was obtained the ^{1}H NMR spectrum of which was identical to that previously reported.[12]

Table 3 Recyclability studies of DES

Entry[a]	Recycling	Yield (%)
1	Fresh	94
2	1	92
3	2	90
4	3	88
5	4	84

[a]These reactions were allowed to run for 30 min and were isolated via extraction with ethyl acetate.

We chose the preparation of pyrrole (**4a**) for studying the recyclability of DES. Thus the DES residue obtained after extraction of (**4a**) with ethyl acetate (see *General experimental procedure*) was dehydrated under vacuum on a rotary evaporator for 15 min and directly used for repeating the reaction. Table 3 presents data obtained after five such recycles. The results indicate that DES can be recycled at least three times without significant loss in activity.

Probable mechanism

Figure 1 depicts a plausible mechanism for this reaction. It is based on a mechanism reported[12a] previously and on the proposed[13] hydrogen bonding capability of urea. Thus condensation of the enaminoketone (**2a'**) formed by reaction of aniline (**2a**) with 1,3-diketone (**3a**) with D-glucose is facilitated by hydrogen bonding of urea with the anomeric hydroxyl group. The resulting aldol product (**3a'**) on subsequent cyclodehydration followed by aromatization affords the annulated pyrrole (**4a**).

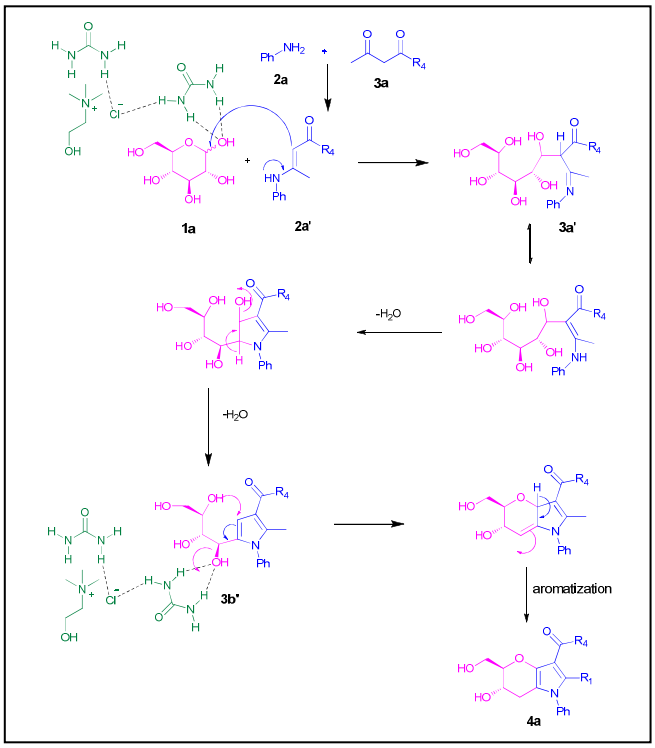

Figure 1

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Conclusion

In summary, we have demonstrated a remarkably simple three component reaction between free sugars, amines and 1,3-dicarbonyl compounds in DES that results in the formation of annulated pyrroles in good yields. This protocol offers additional advantages such as simple workup and general applicability for the synthesis of biologically active pyrrole derivatives.

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14. ***General experimental procedure:***
A mixture of free sugar (**1a, b, c, d**) (5.5 mmol), aryl amine (**2a, b)** (6.11 mmol), 2,4-dione (**3a, b, c)** (6.11 mmol) and CC/U (10 ml) was stirred at 80 °C for 30 min (see Table 1). When the reaction was complete (TLC), the mixture was extracted with ethyl acetate (2×15 mL). The combined organic extracts were washed with H_2O and dried (anhyd Na_2SO_4). Removal of solvent followed by purification by column chromatography (silica gel, EtOAc–n-hexane, 7:3) afforded pure dihydroxy product (**4a-4k**), which was acetylated by using Ac_2O (7.3 mmol) and DMAP (catalytic amount) in CH_2Cl_2 (5 mL). The reaction mixture was stirred at r.t. for 30 min, then poured into ice-water (50 mL) and extracted with CH_2Cl_2 (2 ×25 mL). The combined organic layer was washed with H_2O (2×25mL), dried (anhyd Na_2SO_4) and evaporated to yield pure acetylated products (**5a-5k)** in 84–94% yield.

Notes and references

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