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Multicomponent synthesis of unnatural pyrrolizidines using 1,3-dipolar cycloaddition of proline esters†

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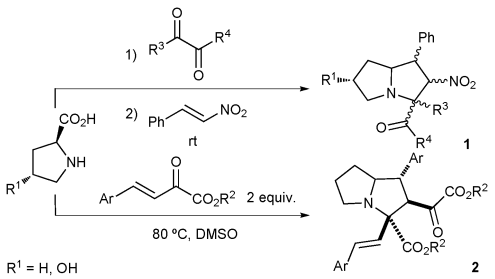
The synthesis of unnatural pyrrolizidines has been studied using a multicomponent-domino process involving proline or 4-hydroxyproline esters, an aldehyde and a dipolarophile. The formation of the iminium salt promotes the 1,3-dipolar cycloaddition affording highly substituted pyrrolizidines under mild conditions and high regio- and diastereoselectivities.

Pyrrolizidine alkaloids are a group of naturally occurring alkaloids[1] produced by plants as a defense mechanism against insect herbivores. The evolution of pyrrolizidine alkaloid biosynthesis highly conserves the first steps of the pathway whilst the diversification of secondary derived pyrrolizidine alkaloids occurs.[2] This process ensures the appearance of new families of pyrrolizidines over time. Many of them are potent hepatotoxic, mutagenic and tumorigenic agents although some families of pyrrolizidines possess interesting therapeutic and medicinal applications. The synthesis of these natural frameworks has been achieved, for example, employing different strategies such as chain elongation of proline derivatives, followed by cyclization,[3] transannular iodoamination,[4] using lactams,[5] from other natural products,[6] *etc.* However, the most important and straightforward route is to employ a 1,3-dipolar cycloaddition (1,3-DC)[7,8] using mainly nitrones[9] or azomethine ylides.[10,11] The characteristic regio- and diastereoselective control of these cycloadditions contributes to the enhancement of the importance of this strategy for this purpose. In particular, proline has been used as starting material for the *in situ* generation of an azomethyne ylide ready to react with an electrophilic alkene (Scheme 1).

In these examples the generation of the reactive dipole proceeds after decarboxylation of the proline, which reduces the functionalization of the resulting pyrrolizidine. The intermediate dipole, generated from 2,3-butanedione or ethyl pyruvate and proline or (2*S*,4*R*)-4-hydroxyproline, has been trapped using β-nitrostyrene. Unexpectedly, the decarboxylation occurred at room temperature



Scheme 1

affording mixtures of pyrrolizidines **1** in good chemical yields (78–90%).[12] More recently, it has been described that the same proline underwent a domino iminium salt formation with β,γ-unsaturated α-keto esters followed by decarboxylation and cycloaddition with the named keto ester at 80 °C in DMSO as solvent.[13]

In this work we describe the multicomponent 1,3-DC between proline esters, aldehydes and dipolarophiles. The generation of the reactive azomethine ylide will be achieved through the iminium salt route[7b] and the cycloaddition will be surveyed at room temperature in the presence or in the absence of silver salts. The aim of this strategy is to maintain the original ester functional group of the proline in order to obtain modified pyrrolizidines with diverse functionalization at the 7a carbon atom of the named fused heterocycle. In this way the access to unnatural alkaloids with unknown biological properties would be ensured.[14]

The synthesis of pyrrolizidines **3** was initially tested at room temperature employing a multicomponent process following the previous methodology developed by our group.[15] Proline methyl ester hydrochloride was allowed to react with cinnamaldehyde and methyl acrylate using triethylamine (1 equiv.). Despite toluene[16] afforded a slower reaction (5 h) with methyl acrylate (96% crude yield of pure **3a**), it was selected as solvent because a higher diastereoselection (99 : 1) was obtained in this example (Scheme 2 and Table 1). Two different processes run in THF (1 h) and DCM (1 h) afforded lower diastereoselectivity of compound **3a** (88 : 12, and 85 : 15, respectively). Different dipolarophiles such as allyl methacrylate, *N*-methylmaleimide (NMM), dimethyl fumarate, β-nitrostyrene, and 1,2-bis(phenylsulfonyl)ethylene afforded the corresponding

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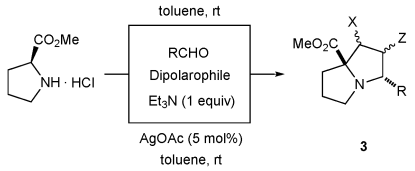
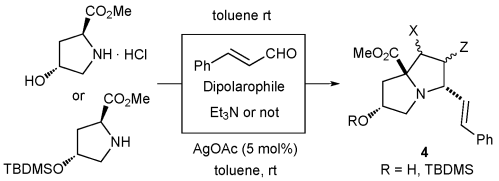
† Electronic supplementary information (ESI) available. Experimental data. CCDC 961250 and 961570. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3cc47184e



Scheme 2



Scheme 3

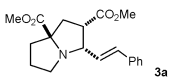
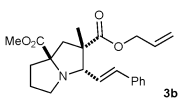
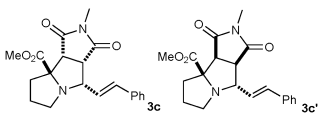
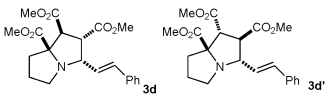
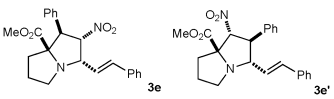
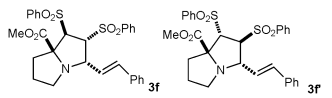
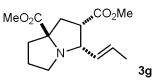
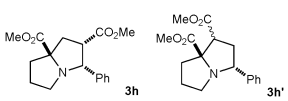
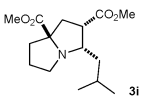
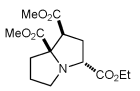
pyrrolizidines **3b–3f** in good yields and high dr (Table 1, entries 2–6). When the 1,3-DC was carried out in the presence of AgOAc (5 mol%) compound **3a** was obtained after 10 h (Table 1, entry 1). Under identical reaction conditions AgTFA, AgOTf and Ag_2CO_3 afforded similar results for compound **3d**. For these reasons the same reactions described above were also performed at rt in the presence of AgOAc (Table 1, entries 2–6).

The reaction in the absence of silver salts is faster than the analogous silver-mediated processes furnishing the same dr (up to 99 : 1). However, higher diastereoselections were achieved in the presence of AgOAc when other aldehydes such as crotonaldehyde, benzaldehyde, isovaleraldehyde and ethyl glyoxylate were used as iminium salt precursors (Table 1, entries 7–10). Moreover, the last two reactions did not proceed in the absence of silver acetate.

All diastereoisomers were separated by column chromatography and the relative configuration of these new compounds was established according to the X-ray diffraction analysis of molecule **3a**[17] and additional nOe experiments performed for other compounds.

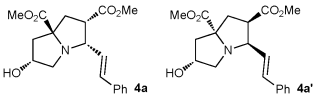
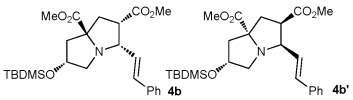
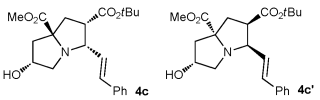
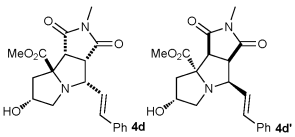
Due to the existence of multiple hydroxy groups as substituents in natural pyrrolizidine alkaloids we surveyed the effect of a stereogenic

Table 1 Synthesis of pyrrolizidines **3** employing L-proline and aldehydes with several dipolarophiles

				Without AgOAc			With AgOAc		
Entry	Aldehyde	Dipolarophile	Product **3**	*t* (h)	Yield[a] (%)	dr	*t* (h)	Yield[a] (%)	dr
1	Cinnamaldehyde	Methyl acrylate	 **3a**	5	(95) 80	99 : 1	10	(94) 80	99 : 1
2	Cinnamaldehyde	Allyl methacrylate	 **3b**	3	(93) 82	99 : 1	8	(93) 81	99 : 1
3	Cinnamaldehyde	NMM	 **3c** **3c'**	2	(92) 80	85 : 15	10	(92) 81	85 : 15
4	Cinnamaldehyde	Dimethyl fumarate	 **3d** **3d'**	2	(96) 83	85 : 15	6	(96) 83	85 : 15
5	Cinnamaldehyde	β-Nitrostyrene	 **3e** **3e'**	2	(95) 79	85 : 15	10	(94) 78	85 : 15
6	Cinnamaldehyde	Disulfone	 **3f** **3f'**	3	(85) 62	62 : 19 : 19[b]	9	(90) 72	72 : 28
7	Crotonaldehyde	Methyl acrylate	 **3g**	1	(96) 85	90 : 10	9	(96) 85	90 : 10
8	Benzaldehyde	Methyl acrylate	 **3h** **3h'**	5	(85) 65	37 : 37 : 26[b]	24	(90) 75	80 : 20
9	Isovaleraldehyde	Methyl acrylate	 **3i**	3	—	—	24	(96) 80	80 : 20
10	Ethyl glyoxylate	Methyl acrylate	 **3j**	6	—	—	24	(88) 59	99 : 1

[a] Isolated yields of the mixture of diastereoisomers (in brackets crude pure yield). [b] The third isomer was not characterized.

Table 2 Synthesis of pyrrolizidines **4** employing (2*S*,4*R*)-4-hydroxyproline and cinnamaldehyde with several dipolarophiles

				Without AgOAc			With AgOAc		
Entry	R	Dipolarophile	Product **4**	*t* (h)	Yield[a] (%)	dr	*t* (h)	Yield[a] (%)	dr
1	H	Methyl acrylate		4	(93) 85	80 : 20	6	(92) 85	87 : 13
2	TBDMS	Methyl acrylate		4	(91) 80	78 : 18	6	(92) 79	80 : 20
3	H	*t*-Butyl acrylate		3	(92) 80	90 : 10	6	(92) 82	98 : 2
4	H	NMM		3	(91) 80	75 : 25	6	(94) 81	75 : 25

[a] Isolated yields of the mixture of diastereoisomers (in brackets crude pure yield).

centre at the 4 position of the heterocycle. Thus (2*S*,4*R*)-4-hydroxyproline and its *O*-TBDMS protected derivative were used as starting materials in the title 1,3-DC with acrylates and NMM employing cinnamaldehyde as the iminium salt precursor (Scheme 3, and Table 2). The *O*-TBDMS protected proline ester furnished compound **4b** in lower diastereoselection than the corresponding reaction performed with (2*S*,4*R*)-4-hydroxyproline methyl ester yielding cycloadduct **4a** (Table 2, entries 1 and 2). *tert*-Butyl acrylate gave product **4c** with higher diastereoselection (98 : 2) than methyl acrylate, especially in the presence of silver acetate (Table 2, entry 3). In the case of NMM products **4d** and **4d′** were obtained in a 4 : 1 diastereomeric ratio (Table 2, entry 4). All the diastereoisomers could be separated by column chromatography providing enantiomerically enriched compounds **4**. Pale yellow needles obtained from molecule **4a** were subjected to X-ray diffraction analysis and served for the determination of its absolute configuration.[18] The relative configuration of the rest of products was assigned according to positive nOe experiments.

We can conclude that a very simple multicomponent 1,3-DC from proline methyl esters, aldehydes and dipolarophiles is an appropriate methodology to prepare highly substituted unnatural pyrrolizidine alkaloids. The corresponding enantiomerically pure 1*H*-pyrrolizidin-2-ol skeleton was prepared from natural (2*S*,4*R*)-4-hydroxyproline methyl ester. The presence of AgOAc was crucial when aliphatic aldehydes and ethyl glyoxylate were employed because the reaction failed under standard conditions.

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