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Efficient Pyrrole Synthesis Using Double Nucleophilic Addition to α,β-Unsaturated Imines with Plural Nucleophiles

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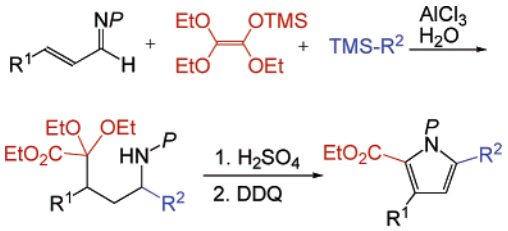
ABSTRACT



2,3,5-Trisubstituted pyrroles were prepared in a regioselective manner using the double nucleophilic addition of α,α-dialkoxy ketene silyl acetals and ketene sily thioacetals or trimethylsilyl cyanide to α,β-unsaturated imines followed by acid-promoted cyclization and oxidation with DDQ. Using this methodology an imidazole glycerol phosphate dehydratase inhibitor (IGPDI) possessing a monopyrrole aldehyde moiety was synthesized.

Widespread existence of biologically important pyrrole derivatives[1] coupled with the need to construct such a skeleton in an efficient manner prompted us to explore a new methodology.[2] A potentially effective approach to construct a pyrrole ring involves cyclization of γ-amino carbonyl compounds followed by dehydrogenation. For the synthesis of γ-amino carbonyl compounds, crucial intermediates in this strategy, nucleophilic addition to γ-oxoimines constitutes a straightforward pathway. However, difficulty has often been encountered for the synthesis of γ-oxoimines due to susceptibility to hydrolysis and/or isomerization.[3] For circumvention of such a drawback of isolating relatively unstable imine intermediates as well as use of an operationally simple experimental procedure, we have recently introduced a double nucleophilic addition reaction to α,β-unsaturated imines.[4] When α,α-dialkoxy ketene silyl acetal, an acyl anion equivalent, is used as the first nucleophile, this methodology offers a facile synthetic route to γ-amino carbonyl synthons. This paper describes a straightforward

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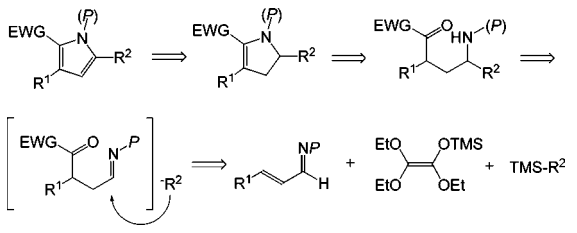
approach to γ-amino carbonyl compounds and the subsequent transformation into 2,3,5-trisubstituted pyrroles (Scheme 1),

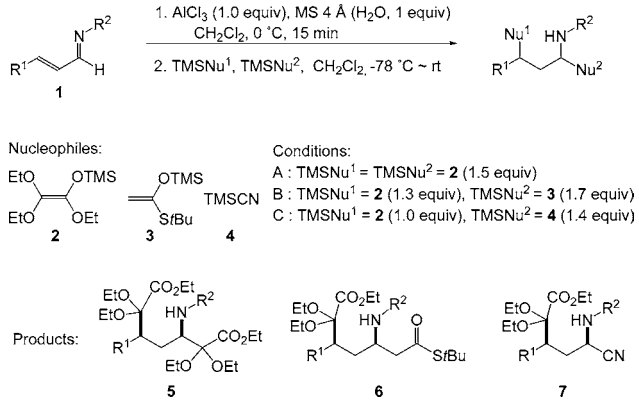
Scheme 1. Present Strategy for the Synthesis of Pyrroles



which enables a six-step synthesis of imidazole glycerol phosphate dehydratase inhibitors (IGPDIs) of herbicidal activity.[5]

For the synthesis of γ-amino carbonyl compounds, an initial reaction was carried out using imine **1** and ketene silyl acetal **2** (3.0 equiv) in CH_2Cl_2 in the presence of aluminum chloride (1.0 equiv) and MS 4Å containing H_2O at −78 °C to room temperature to give the double addition product **5** in good yield with *syn*-selectivity (Table 1, conditions A).

Table 1. Double Nucleophilic Addition to α,β-Unsaturated Imines **1**[a]



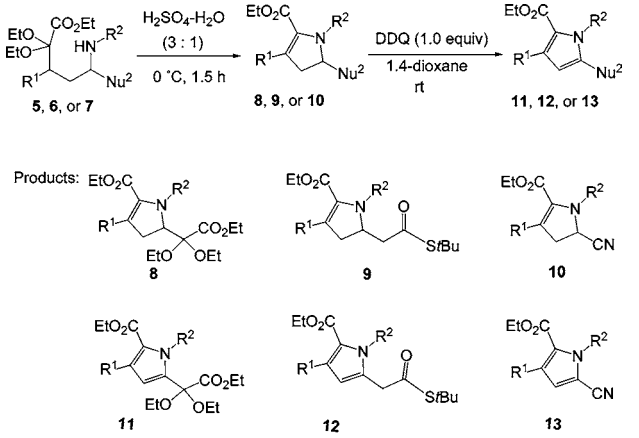
entry	R^1	R^2	conditions	time (h)	product	(%)[b]	*syn*:*anti*[c]
1	Ph	PMP	A	8.5	**5a**	85	87:13
2	Ph	Ph_2CH	A	9.5	**5b**	80	75:25
3	Ph	4-$Me_2NC_6H_4$	A	13.0	**5c**	66	76:24
4	Me	PMP	A	9.5	**5d**	90	99: 1
5	Ph	PMP	B	11.5	**6e**	80	90:10
6	Ph	4-$Me_2NC_6H_4$	B	14.0	**6f**	63	55:45
7	Ph	2,4-$(MeO)_2C_6H_3$	B	14.0	**6g**	62	85:15
8	Me	PMP	B	14.0	**6h**	70	67:33
9	Ph	PMP	C	17.0	**7i**	55	94: 6
10	Me	PMP	C	16.0	**7j**	95	88:12

[a] See typical procedure. [b] Isolated yields. [c] Determined by HPLC and/or ^{1}H NMR.

The 4-methoxyphenyl (PMP) or diphenylmethyl group at the nitrogen atom was the substituent of choice for the double addition acceptors (Table 1, entries 1, 2, and 4). The best diastereomeric excess was obtained using *N*-4-methoxycrotylidenimine (entry 4). Use of the 4-dimethylaminophenyl derivative recorded both a decreased product yield and a diastereomeric excess presumably due to the coordination of the nitrogen atom of the 4-dimethylaminophenyl group with $AlCl_3$ (entry 6). We next examined use of ketene silyl thioacetal **3** (Table 1, conditions B) or trimethylsilyl cyanide **4** (Table 1, conditions C) as the second nucleophile, with ketene silyl acetal **2** as the first nucleophile to give the double addition product **6** or **7**, respectively. The reactions proceeded regio- and chemoselectively. We found that the ketene silyl acetal **2** underwent 1,4-addition, whereas the ketene silyl thioacetal **3** or trimethylsilyl cyanide **4** underwent 1,2-addition in a highly regioselective manner, where the only byproduct obtained was a negligible amount of 1,2-addition product derived from **1** with **2**.

All the 1,4- and 1,2-addition products obtained were converted readily into the corresponding multisubstituted pyrroles via cyclization into dihydropyrrole with acids such as H_2SO_4, methanesulfonic acid, and TFA followed by dehydrogenation with DDQ (Table 2). Both steps proceeded to give the products in high yield. Cyclization of the adduct **5b** needed a slightly longer reaction time for completion in

Table 2. Transformation into Dihydropyrrole and Pyrrole[a]



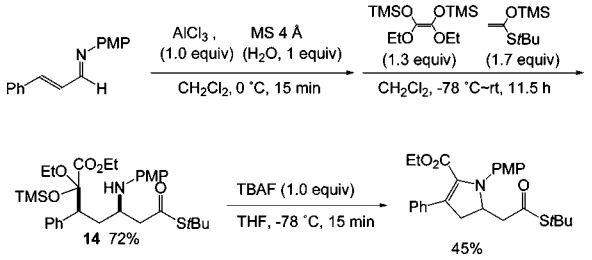
entry	**5**,**6**,**7**	dihydropyrrole	(%)[b]	time (h)[c]	pyrrole	(%)[b]
1	**5a**	**8a**	88	13.0	**11a**	quant
2	**5b**	**8b**	96	13.0	**11b**	95
3	**5c**	**8c**	quant	13.0	**11c**	quant
4	**5d**	**8d**	69[d]	13.0	**11d**	66
5	**6e**	**9e**	73	12.5	**12e**	62
6	**6f**	**9f**	67[e]	12.5	**12f**	93
7	**6g**	**9g**	79[e]	12.5	**12g**	97
8	**6h**	**9h**	86	12.5	**12h**	69
9	**7i**	**10i**	quant[e]	12.0	**13i**	74
10	**7j**	**10j**	86[e]	12.0	**13j**	80

[a] See typical procedure. [b] Isolated yields. [c] Time for dehydrogenation. [d] H_2SO_4:H_2O = 2:1. The reaction time was 6.5 h. [e] H_2SO_4:H_2O = 1:1.

the presence of a 2:1 mixture of H_2SO_4 and H_2O (entry 4). Regarding the instances where the cyclization was relatively harsh, use of increased amounts of H_2O improved the product yields (entries 6, 7, 9, and 10). Subsequent dehydrogenation with DDQ proceeded to give pyrroles in good to excellent yields.

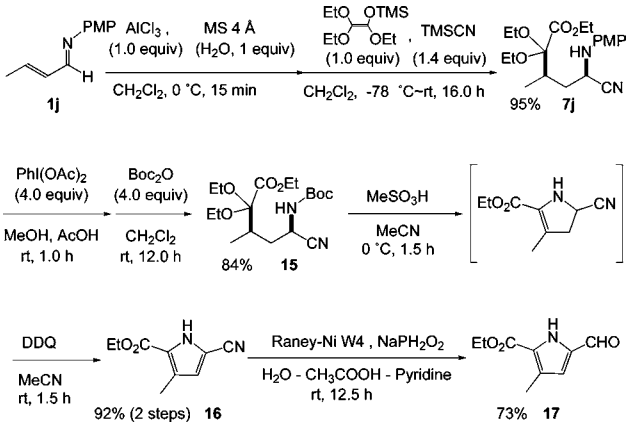
A similar cyclization into dihydropyrrole was effected by TBAF, albeit in moderate yield, when the TMS ether derivative **14** prepared from 1,2-bis(trimethylsiloxy)-1,2-diethoxyethene was used (Scheme 2).

Scheme 2. Cyclization Effected by TBAF



As an application of the present methodology, a synthesis of the IGPDI **17** possessing herbicidal activity[6] was carried out (Scheme 3). The ketene silyl acetal **2** and trimethylsilyl cyanide **4** were treated with *N*-4-methoxycrotylidenimine **1j** in the presence of $AlCl_3$ to give the doubly alkylated product **7j** in 95% yield (see Table 1, entry 10). Removal of the PMP group was carried out by oxidation with $PhI(OAc)_2$[7] followed by the protection of the formed amine functionality with a Boc group because of the difficulty in removing of PMP group after cyclization into the pyrrole. The Boc-protected double-addition product **15** was treated with $MeSO_3H$ and DDQ to afford the pyrrole **16** in 92% yield (2 steps), where the NH-free dihydropyrrole intermediate was not isolated. Finally reduction of the cyano group with Raney-Ni W4 in the presence of $NaPH_2O_2$[8] gave the desired monopyrrole aldehyde **17** in 73% yield.

Scheme 3. Synthesis of IGPDI



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Supporting Information Available: Experimental procedures and product characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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