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Synthesis of 2*H*-pyrroles by treatment of pyrrolidines with DDQ

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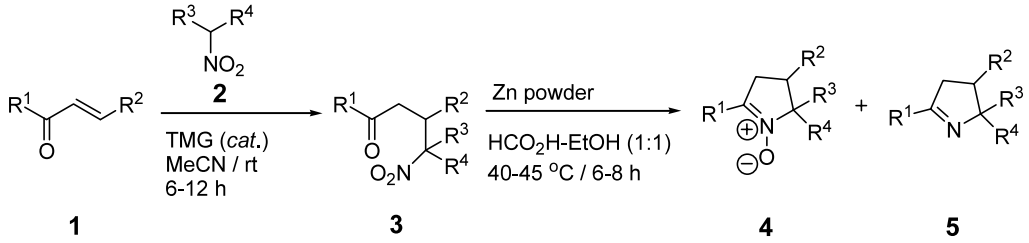
Abstract—A mild and efficient synthesis of 2,2-dialkyl-3,5-diaryl-2*H*-pyrroles is described. Treatment of 2,2-dialkyl-3,5-diarylpyrrolidines with DDQ in dioxane for 12–24 h at rt afforded the corresponding 2*H*-pyrroles in 55–81% overall yields.

In our ongoing search for novel classes of biologically active heterocycles, we became interested in the exploration of the 2*H*-pyrrole framework. There are five general routes for synthesis of 2*H*-pyrroles: (i) electrophilic addition to C-2 monosubstituted 1*H*-pyrroles and subsequent isomerization;[1] (ii) 1,3-dipolar cycloaddition of azomethine ylides to alkynes followed by dehydrogenation;[2a–e] (iii) cyclocondensation of amines or azaallyl anions with ketones;[3a–c] (iv) reaction of vinylic derivatives with nitrenes generated in situ by thermolysis of 3-vinylazirines;[4a–e] and (v) reductive cyclization of γ-nitroketones to 2*H*-pyrroles via 1-pyrroline oxides or 1-pyrrolines.[4c,5a–d]

For our 2*H*-pyrrole synthesis, we selected the reductive cyclization route as a general synthetic strategy[5c] in view of the structural diversity of the many chalcones **1** that can be easily obtained from the many commercially available and relatively inexpensive starting material acetophenones and benzaldehydes.[6] Conjugate addition of secondary nitroalkanes **2** to the chalcone intermediates **1** was carried out using tetramethylguanidine (TMG) in dry CH_3CN (Scheme 1).[7] Reductive cyclization of the resulting γ-nitroketones **3** with Zn/HCOOH–EtOH invariably produced a mixture of pyrroline *N*-oxides **4** and pyrrolines **5**.[4c,5a–d] More conveniently, however, we cleanly obtained the corresponding pyrrolidines **6** by treatment of γ-nitroketones **3** with nickel catalyst (Raney® 2800 nickel) in ethanol at room temperature under a hydrogen atmosphere (Scheme 2).[8] Treatment of these pyrrolidine intermediates **6a–h** with DDQ (2.2 equiv.) in dioxane at room temperature afforded the desired 2*H*-pyrroles **7a–h** in 55–81% yields, and the reaction appeared to be quite general (Scheme 2, Table 1). Initial trials using dry benzene as solvent were unsatisfactory. At least 2 equiv. of DDQ were required to drive the reaction to completion. One critical advantage of this method is that no isomeric 1*H*-pyrroles were formed.

DDQ is very commonly used for aromatization of carbocyclic and fused heterocyclics, but in only one case[9] was this reagent applied to the conversion of pyrrolines to 2*H*-pyrroles. Other reagents such as the closely related chloranil[3b,9] and MnO_2[9,10] tend to form isomeric mixtures of 1*H*- and 2*H*-pyrroles due to sigmatropic rearrangements at the elevated reaction tem-



Scheme 1.

Keywords: DDQ; reductive cyclization; γ-nitroketones; pyrrolines; pyrroldines; 2*H*-pyrroles.
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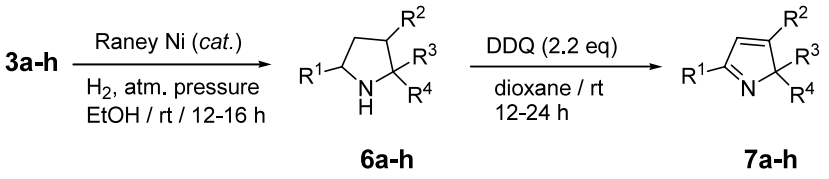

Scheme 2.

Table 1. Synthesis of 2*H*-pyrroles (**7a–h**) from pyrrolidines (**6a–h**)

Pyrrolidine	R^1	R^2	R^3	R^4	2*H*-Pyrrole	Yield (%)	Mp (°C)[a]
6a	C_6H_5	C_6H_5	CH_3	CH_3	**7a**	81	58–60 (59–61)[4b]
6b	C_6H_5	C_6H_5	-$(CH_2)_4$-		**7b**	72	97–99
6c	C_6H_5	C_6H_5	-$(CH_2)_5$-		**7c**	67	109–111 (112–114)[4b]
6d	C_6H_5	4-CH_3-C_6H_4	CH_3	CH_3	**7d**	71	85–87 (275)[12]
6e	C_6H_5	4-Pyridyl	CH_3	CH_3	**7e**	69	111–113 (115)[5c]
6f	4-Pyridyl	C_6H_5	CH_3	CH_3	**7f**	74	89–91 (93–94)[13]
6g	4-CH_3-C_6H_4	C_6H_5	CH_3	CH_3	**7g**	55	82–84 (270)[12]
6h	4-CH_3-C_6H_4	4-CH_3-C_6H_4	CH_3	CH_3	**7h**	78	91–93 (285)[12]

[a] Literature values in parentheses for known 2*H*-pyrroles or the corresponding hydrochloride salts.

peratures. Interestingly, few reports[11a–e] describe dehydrogenation of pyrrolidines to pyrrolines or 1*H*-pyrroles; to our knowledge the direct conversion of pyrrolidines to 2*H*-pyrroles has yet to be documented.

Typical procedure: To a stirred solution of pyrrolidine **6a** (5.0 mmol) in dioxane (20 ml) at room temperature was added DDQ (11.0 mmol). The reaction mixture immediately turned deep green, and it was allowed to stir until the starting material was consumed (16 h in this case). The solvent was removed in vacuo, and dry benzene (15 ml) was added to the resulting residue and the insoluble hydroquinone was filtered. It was rinsed with benzene (2×10 ml) and the combined filtrates were concentrated under reduced pressure to give a dark brown oil. Crystallization of this crude material from benzene:hexanes (2:1) afforded 2*H*-pyrrole **7a** as a colorless solid.

In conclusion, a mild and direct method was developed for the conversion of pyrrolidines to 2*H*-pyrroles, thus expanding the utility of the reductive cyclization route.

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