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Activated pyrroles from pyridazines: nitrogen extrusion by electroreduction

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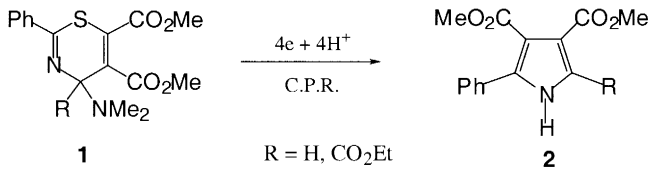
Abstract

The bielectronic electrochemical reduction of pyridazines, substituted by electron-withdrawing groups, leads to their corresponding 1,2-dihydro derivatives. Depending on the nature of the ring substitution, these intermediates can either rearrange into 1,4-dihydropyridazine isomers or be further electrochemically reduced into activated pyrroles.

Keywords: electrochemical reduction; pyridazine; ring contraction; dihydropyridazine; pyrrole; nitrogen extrusion.

Ring transformation of heterocycles appears to be an efficient methodology to produce pyrrole derivatives.[1] We have previously shown that substituted pyrroles can be obtained by sulfur extrusion from 1,3-thiazine heterocycles[2] by an electrochemical reduction process.[3,4] In particular, functionalized pyrroles **2** were isolated from the 4*H*-1,3-thiazines **1** following this procedure (Scheme 1).[5,6]



1 **2**

Scheme 1.

The presence of the heterocyclic nitrogen atom is crucial for the above extrusion process to be achieved since no ring contraction occurred in the same conditions from 4*H*-thiopyran analogues.[7] Nitrogen extrusion from six membered azaheterocycles has also been investigated as an attractive way to produce substituted pyrroles.[1] Although reductive ring contraction of activated pyridazine derivatives was successfully performed by chemical reduction,[8,9] only a few studies using electrochemical procedures

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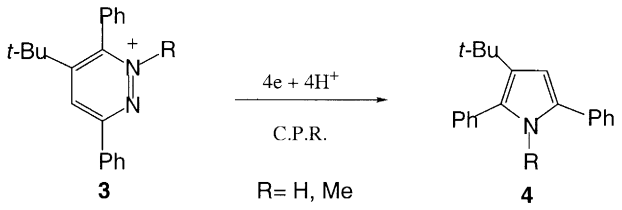
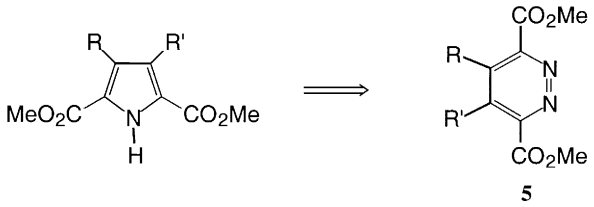
have been reported. In the latter approach, a mixture of two pyrroles **4** was obtained by Lund from the pyridazinium cation **3** (Scheme 2).[10,11]

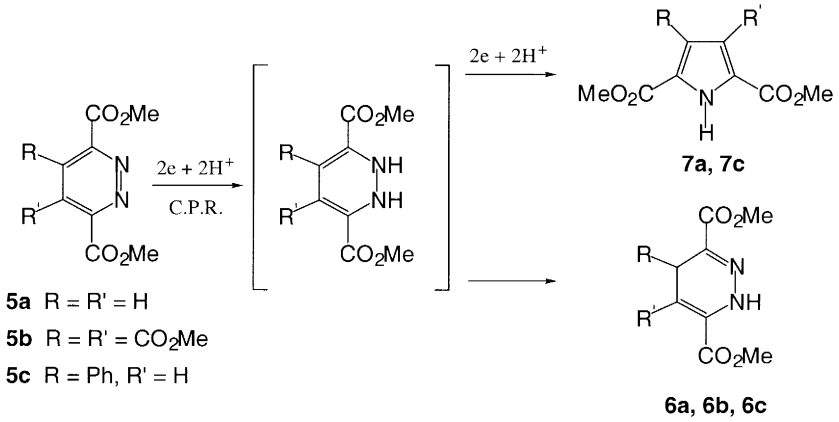


Scheme 2.

Taking into account these results, we proceeded to evaluate the potential of activated pyridazines **5** to give the corresponding functionalized pyrroles by an electrochemical reduction process (retrosynthesis).



Substituted pyridazines **5a**–**5c** were first prepared by a convergent synthesis from 1,2,4,5-tetrazine-3,6-dicarboxylic acid dimethyl ester.[12] The influence of the nature of the substituent groups on the electrochemical behavior of the pyridazine precursors has been examined (Scheme 3). The polarographic experiments and the preparative electrolysis were performed in acetate buffer.[13]



Scheme 3.

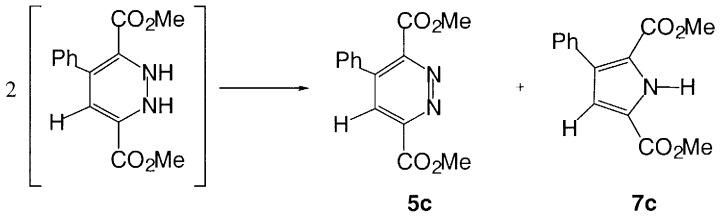
(a) Pyridazine-3,6-dicarboxylic acid dimethyl ester **5a**[14] is reducible in three successive bielectronic steps ($E_{1/2}$=−0.69; −0.86 and −1.07 V/SCE). Preparative electrolysis, carried out under nitrogen atmosphere at the potential of the first wave, leads quantitatively to the 1,4-dihydropyridazine derivative **6a**, which can be further reduced at the level of the third wave. Controlled potential reduction (CPR) at the plateau of the second wave (E=−1.0 V/SCE) gives rise to the formation of the 1*H*-pyrrole-2,5-dicarboxylic acid dimethyl ester **7a**,[15–17] in 60% yield, beside some starting material **5a** resulting from air oxidation of the 1,4-dihydro derivative **6a** during the reaction work up (Scheme 3).

(b) Pyridazine-3,4,5,6-tetracarboxylic acid tetramethyl ester **5b**[14] shows only two bielectronic reduction waves at $E_{1/2}$=−0.45 and −1.05 V/SCE (to be compared with the first and the third waves for com-

pound **5a**). The electroreduction at −0.7 V/SCE yields quantitatively the 1,4-dihydropyridazine-3,4,5,6-tetracarboxylic acid tetramethyl ester **6b**[18] (Scheme 3). This compound appears to be further reducible at a more negative potential. However, the corresponding 1*H*-pyrrole derivative **7b** was not obtained. Due to our objective, focused on possible access to pyrroles **7**, reduction of the 1,4-dihydropyridazines **6** has not been investigated.

(c) Polarographic reduction of the 4-phenyl-pyridazine-3,6-dicarboxylic acid dimethyl ester **5c**[14] displays three successive waves at $E_{1/2}$=−0.72 (higher than a two electron reduction wave); −0.86 (lower than a two electron wave) and −1.03 V/SCE (corresponding to a bielectronic process). Such a behavior clearly indicates a disproportionation of the two electron reduction product (vide infra). However, the preparative electrolysis, carried out in the range of −0.7 to −0.9 V/SCE, always leads to a mixture of the corresponding 1,4-dihydropyridazine **6c**[19] and 3-phenyl-1*H*-pyrrole-2,5-dicarboxylic acid dimethyl ester **7c**[9,17](Scheme 3). The best yield (70%) in pyrrole is obtained at more negative potential (−0.9 V/SCE). This result can be compared with the chemical reduction path (zinc in acidic medium), yielding the pyrrole **7c** at 65%.[12]

As a conclusion, electroreduction of pyridazines **5** is governed by the chemical behavior of the 1,2-dihydro intermediate, resulting from the two electron reduction process: (i) if the rearrangement of the 1,2-dihydro intermediate into the corresponding 1,4-isomer derivative (series **b**) is very fast, the formation of pyrrole **7** is not observed; (ii) if this rearrangement is slow enough (series **a**), pyrrole can be formed when electroreduction is performed at the plateau of the second polarographic wave; (iii) however, disproportionation of the 1,2-dihydropyridazine remains possible (series **c**) leading to an equimolecular mixture of pyrrole **7c** and starting compound **5c** (Scheme 4).This reaction is thus in competition with the prototropy event giving the dihydropyridazine **6c**



5c **7c**

Scheme 4.

Such an interpretation must be correlated with complementary investigations which should be run from other pyridazine precursors. In particular, experiments from pyridazine-3,6-dicarboxylic acid dimethyl ester derivatives carrying electron-donating substituents at the 4 and/or 5 position must be investigated. However, we have already demonstrated the possibility of formation of functionalized 1*H*-pyrroles by electrochemical reduction of activated pyridazines. Thus, nitrogen extrusion from pyridazine-3,6-dicarboxylic acid dimethyl ester through an electroreduction process leads to substituted 1*H*-pyrrole **7c**, a structural isomer of the 1*H*-pyrrole **2** (R=H).

Acknowledgements

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13. For a typical procedure see Ref. 6. Controlled potential electrolysis is carried out at a mercury pool cathode.
14. For the synthesis of pyridazines **5a**, **5b** and **5c** see, respectively: (a) Sauer, J.; Mielert, A.; Lang, D.; Peter, D. *Chem. Ber.* **1965**, 1435–1445. (b) Neunhoeffer, H.; Werner, G. *Liebigs Ann. Chem.* **1973**, 437–442. (c) Ref. 12.
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17. 1*H*-Pyrrole derivatives **7a**[15,16] and **7c**[9] exhibited spectroscopic data (^{1}H NMR, IR, MS) and combustion analyses in agreement with the structures assigned. Selected data for **7a**: ^{13}C NMR (50.3 MHz, $CDCl_3$) δ ppm 51.9 (q, *J*=147 Hz, CO_2CH_3), 115.5 (d, *J*=177 Hz, C-3, C-4), 126.0 (C-2, C-5), 160.7 (CO_2CH_3). For **7c**: ^{13}C NMR (50.3 MHz, $CDCl_3$) δ ppm 51.5 and 51.8 (*J*=147 Hz, CO_2CH_3), 116.5 (*J*=170 Hz, C-4), 127.2, 127.6, 129.1 and 132.2 (Ph), 121.0, 124.5 and 133.7 (C-5, C-3 and C-2), 160.5 (CO_2CH_3).
18. 1,4-Dihydropyridazine-3,4,5,6-tetracarboxylic acid tetramethyl ester **6b**: m.p.=126–127°C (from petroleum ether). ^{1}H NMR (200 MHz, $CDCl_3$) δ ppm 3.7 and 3.8 (2s, 6H, OCH_3), 3.9 (1s, 6H, OCH_3), 5.02 (s, 1H, CH), 9.26 (s, 1H, NH); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ ppm 36.9 (d, *J*=140 Hz, C-4), 52.2, 52.7, 52.9 and 53.3 (4q, *J*=148 Hz, OCH_3), 98.0, 132.1 and 136.9 (C-3, C-5 and C-6), 162.8, 163.4, 164.8 and 169.0 (CO_2CH_3). ν_{max} cm^{-1}: 3275, 3225, 1775, 1750, 1640, 1610. MS *m/z* (%): 314 (CI, M^+), 256 (10), 255 (97), 224 (11), 223 (100), 167 (12), 137 (10), 59 (22). Elemental analysis: $C_{12}H_{14}N_2O_8$; calcd: C, 45.87; H, 4.49; N, 8.91; found: C, 45.84; H, 4.48; N, 8.83.
19. For chemical synthesis of 4-phenyl-1,4-dihydropyridazine-3,6-dicarboxylic dimethyl ester **6c** see Ref. 14a. Selected data: ^{13}C NMR (50.3 MHz, $CDCl_3$) δ ppm 37.7 (d, *J*=136 Hz, C-4), 52.7 and 52.9 (2q, *J*=140 Hz, $2CO_2CH_3$), 110.7 (d, *J*=173 Hz, C-5), 127.9, 128.1, 128.4, 129.2, 133.0 and 142.7 (Ph, C-3 and C-6), 162.2, 164.9 (CO_2CH_3).