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Facile Preparation of Hexahydropyrrolo[3,2-*e*][1,4]diazepine-2,5-diones and Tetrahydrofuro[1*H*][3,2-*e*][1,4]diazepine-2,5-diones by Rearrangements of Cyclopropylketimines and Cyclopropylketones†

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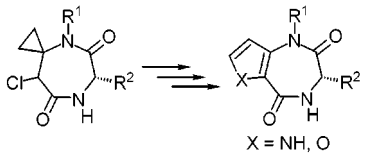
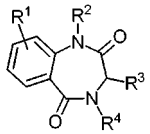
ABSTRACT



Chlorolactames 2a–f reacted with sodium azide to give the cyclopropylketimines 3a–f (75–89%), and acid hydrolysis of 3c,d yielded the cyclopropylketones 6c,d (61–67%). Compounds 3a–f and 6c,d were transformed by heating (170–240 °C, sublimation) to the air-sensitive dihydropyrroles 4a–f (51–71%) and dihydrofurans 7c,d (85–91%). Oxidation of the dihydro derivatives 4a–f and 7c,d with DDQ led to novel types of pyrrolo[3,2-*e*][1,4]diazepinedione derivatives 5a–f (75–84%) and furo[1*H*][3,2-*e*][1,4]diazepinediones 8c,d (91–93%).

A wide range of compounds with the skeleton of tetrahydro-[1*H*][1,4]benzodiazepine-2,5-dione **1** are well-known for their interesting biological activities.



1

Natural products containing this ring system are the nephrotoxic (+)-iforrestine[1] and the antitumor antibiotic oxotomaymycin.[2] Synthetic derivatives have shown anxiolytic,[3] anticonvulsive,[4] antitumor,[5] and antithrombotic activities.[6] Moreover, they have been found to possess fungicidal and plant growth regulating activities[7] and have been evaluated for their herbicidal activity.[8] Althouth the elaboration of

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various substitution patterns of **1** is well established,[9] only a limited number of the reported examples of such compounds contain imidazo, pyrido, or thieno moieties instead of the more common benzo ring.[9t,10] In this communication we wish to report an approach to new types of pyrrolo- and furo-condensed perhydro[1,4]diazepine-2,5-diones.

The new synthesis of hexahydropyrrolo[3,2-*e*][1,4]diazepine-2,5-diones and tetrahydrofuro[1*H*][3,2-*e*][1,4]diazepine-2,5-diones starts with the chlorolactames **2a**−**d** and (2′*S*,6′*S*)-**2e**,**f**,[11] which were cleanly converted in good yields (75−89%) directly to the imines **3a**−**f** by treatment with sodium azide in DMSO (Table 1). It was surprising that these

Table 1. Yields of Imines **3**, Dihydropyrrole Derivatives **4**, and Hexahydropyrrolo[3,2-*e*]-[1,4]diazepine-2,5-diones **5** (see Scheme 1)

			yield (%)		
entry	R^1	R^2	**3**	**4**	**5**
a	*n*-pentyl	H	89	71[a]	84
b	2-furfuryl	H	75	69[b]	75
c	4-MeO(C_6H_4)CH_2	H	77	62	80
d	4-Cl(C_6H_4)CH_2	H	82	64[b]	83
e	Me	CH_2CH_2SMe	82	51[a]	77
f	Me	*i*-Bu	85	59[a]	82

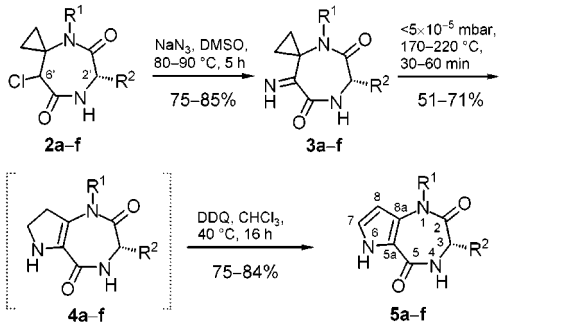
[a] Crude product. [b] Contains 5% of starting material **3** according to the ^{1}H NMR spectrum.

nucleophilic substitutions by azide were so easily succeeded by elimination of nitrogen under the applied conditions.[12] The structural assignments of **3a**−**f** were made on the basis of their spectral data and corroborated by an X-ray crystal structure analysis of the 2-furfuryl-substituted derivative **3b**.[13]

The Cloke rearrangements[14] of the cyclopropylketimines **3** could not be brought about under the usual acid catalysis. Better results were obtained when **3c** was heated in a small sublimation apparatus at 180 °C for 5 min followed by sublimation onto the coldfinger under reduced pressure (<5 × 10^{-5} mbar, 170 → 240 °C). This gave **4c** in 62% yield, and under the same or slightly modified conditions, the other 1-substituted dihydropyrrole derivatives **4a**,**b**,**d** were also obtained in good yields (64−71%) (Table 1). Interestingly, the rearrangement of **3e** and **3f** did only occur at higher temperature (220 °C), and gave the 1,3-disubstituted derivatives **4e** and **4f** as crude products in lower yields (51−59%).

When the air-sensitive compounds **4a**−**f** were treated with 1,2-dichloro-5,6-dicyanobenzoquinone (DDQ) in chloroform at 40 °C, the 1,2,3,4,5,6-hexahydropyrrolo[3,2-*e*][1,4]-diazepine-2,5-diones **5a**−**f** were obtained in good yields (75−84%),[15] and the structure of **5c** was unequivocally proved by X-ray crystal structure analysis[13] (Scheme 1). Acid

Scheme 1



hydrolysis of the substituted benzyl derivatives **3c** and **3d** yielded the ketones **6c** (67%) and **6d** (61%). Thermal rearrangement of the cyclopropylketones **6**[14] using the same experimental setup at 200 °C afforded the dihydrofuran derivatives **7c** and **7d** in very good yields (85−91%). Compounds **7c**,**d** were found to be more stable than the

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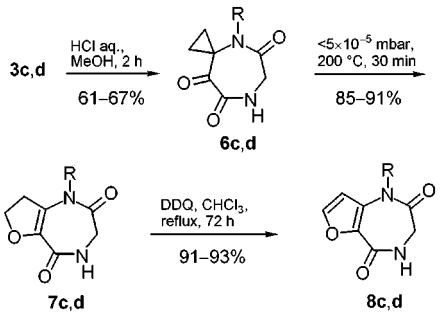
(11) (a) General procedure for the synthesis of these compounds, see: Belov, V. N.; Funke, C.; Labahn, T.; Es-Sayed, M.; de Meijere, A. *Eur. J. Org. Chem.* **1999**, 1345−1356. Overall yields from methyl 2-chloro-2-cyclopropylideneacetate: **2b** (55%), **2c** (53%), **2d** (61%), **2e** (20%), **2f** (19%). (b) Better yields of chlorolactames **2** were obtained using NH_3/MeOH instead of $NaHCO_3$ aq/CH_2Cl_2: Limbach, M.; de Meijere, A., unpublished results.

(12) For a previous example of this kind of reaction, see: Makosza, M.; Sienkiewicz, K.; Wojciechowski, K. *Synthesis* **1990**, 850−852.

(13) The structures were solved by direct methods (SHELXS-93/97) and refined on F^2 by full matrix least-squares techniques (Sheldrick, G. M.; *SHELXL-93/97*, Program for Crystal Structure Refinement, Universität Göttingen, Germany, 1997). Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-141906 for **3b** and CCDC-141907 for **5c**. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. [Fax: int. code +44(1223) 336-033; E-mail: deposit@ccdc.cam.ac.uk].

Scheme 2



corresponding dihydropyrroles **4a**−**f**, and oxidation with DDQ occurred more slowly in refluxing chloroform, affording 2,3,4,5-tetrahydrofuro[1*H*][3,2-*e*][1,4]diazepine-2,5-diones **8c** (91%) and **8d** (93%)[15] (Scheme 2, Table 2).

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Table 2. Yields of Ketones **6**, Dihydrofuran Derivatives **7**, and Tetrahydrofuro[1*H*][3,2-*e*][1,4]diazepine-2,5-diones **8** (see Scheme 2)

		yield (%)		
entry	R	**6**	**7**	**8**
c	4-MeO(C_6H_4)CH_2	67	91	91
d	4-Cl(C_6H_4)CH_2	61	85	93

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Supporting Information Available: Experimental details and full characterization of all new compounds **3**−**8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) These compounds are being tested for biological activity.