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# Diastereoselective Cascade Assembly of Functionalized Pyrano[3,4-*c*]pyrrole Derivatives

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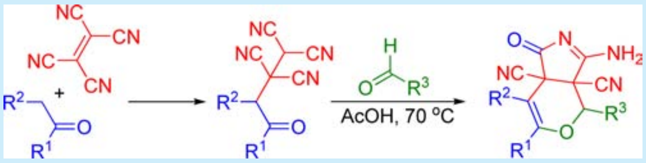
*Supporting Information*

**ABSTRACT:** A novel convenient approach for the synthesis of densely functionalized pyrano[3,4-*c*]pyrrole derivatives was developed. Cascade transformation of the simple adducts of tetracyanoethylene (TCNE) and ketones (4-oxoalkane-1,1,2,2-tetracarbonitriles) in the presence of aldehyde under the action of acetic acid led to the diastereoselective formation of targeted pyrano[3,4-*c*]pyrroles. The reaction pathway was thoroughly investigated, and proposed intermediates were shown to be consistent with experiment.



Pyrano[3,4-*c*]pyrrole derivatives are an uncommon group of fused ring heterocycles. However, such a moiety is counted among the biologically important molecules (Figure 1), for example, dopamine-D3-receptor antagonists,[1] $\alpha$1-adrenoceptor antagonists,[2] and antagonists of 5-HT2C receptors with respect to 5-HT2A3. Pyrano[3,4-*c*]pyrrole derivative named *Fiduxosin* is suggested as a promising pharmaceutical agent for the treatment of benign prostatic hyperplasia.[4] Pyrano[3,4-*c*]pyrrole derivatives are also found to be the inhibitors of the Wnt and Hedgehog signaling pathways.[5] Moreover, a series of publications show that some pyrano[3,4-*c*]pyrrole derivatives are promising organocatalysts.[6]

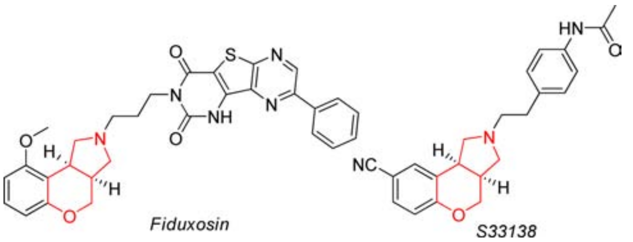
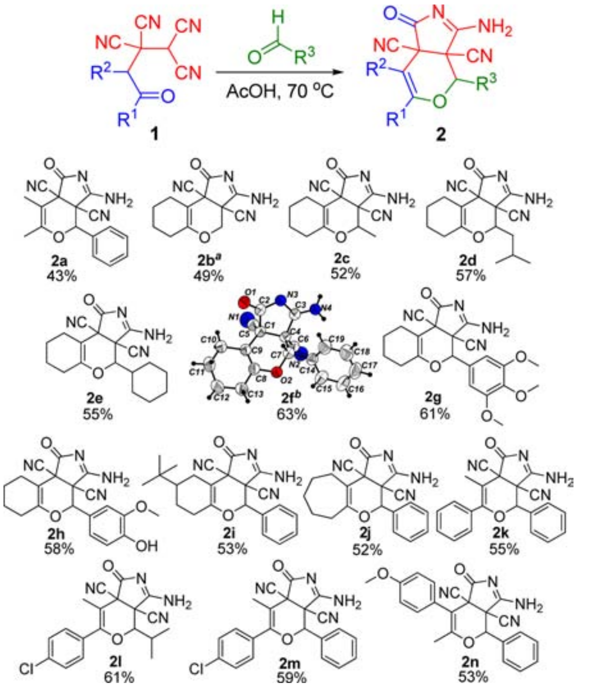


**Figure 1.** Biologically important pyrano[3,4-*c*]pyrrole derivatives.

We have developed a new approach to the synthesis of densely functionalized pyrano[3,4-*c*]pyrrole derivatives. 4-Oxoalkane-1,1,2,2-tetracarbonitriles **1**, the simple and reactive adducts of tetracyanoethylene (TCNE) and ketones, were used as starting compounds, which are long-established promising reagents for the convenient synthesis of inaccessible heterocycles.[7]

The preparation of pyrano[3,4-*c*]pyrrole derivatives **2** proceeds while carefully heating the equimolar mixture of appropriate tetracyanoketone **1** and aldehyde in glacial acetic acid (Scheme 1).

**Scheme 1. Synthesis of Pyrano[3,4-*c*]pyrrole Derivatives 2**



[a]Reaction was carried out with 35% aqueous solution of formaldehyde. [b]X-ray structure of **2f**.

It should be noted that despite the presence of stereogenic centers in both the starting compounds and intermediates, the cascade assembly of the pyrano[3,4-*c*]pyrrole moiety is extremely diastereoselective. Moreover, the wide scope of the

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substituents $R^1$, $R^2$, $R^3$ shows the high synthetic potential of the proposed approach.

The structure of all heterocycles **2** was assigned on the basis of $^1$H, $^{13}$C NMR and IR spectroscopy and HRMS. In addition, the structure of pyrano[3,4-*c*]pyrrole derivatives **2** is further supported by the X-ray diffraction analysis of **2f**, which unambiguously confirmed its structure (see Supporting Information). $^1$H NMR spectra of compounds **2** are characterized by two individual downfielded signals of NH-protons in the area of 9−10 ppm. Such a nonequivalence of amino group protons is probably caused by the dimerization of compounds and formation of hydrogen bonds between the amino group and pyrrolic nitrogen atom. The probability of such hydrogen bonding in the NMR sample is supported by the observed hydrogen bonding in the solid state (Figure 2).

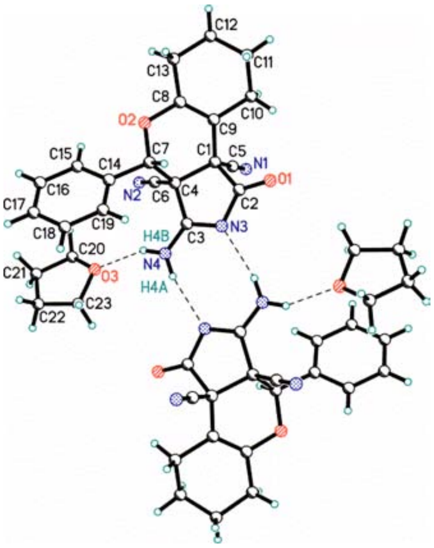
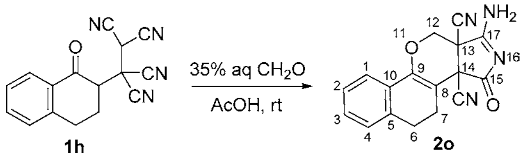


**Figure 2.** Dimeric associations in crystal of compound **2f**.

Easy interaction of tetracyano-substituted $\alpha$-tetralone **1h** with a water solution of formaldehyde should be noted individually. It occurs in acetic acid at room temperature and leads to the formation of compound **2o** with a previously undescribed 11-oxa-16-azasteroid ring system (Scheme 2).

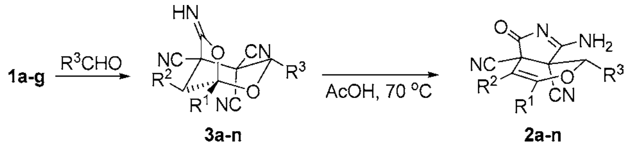
**Scheme 2. Synthesis of Novel 11-Oxa-16-azasteroid Ring System**



According to the $^1$H and $^{13}$C NMR spectra the result of cascade assembly of the pyrano[3,4-*c*]pyrrole moiety is only one of the conceivable diastereomers. The cause of such an asymmetric induction probably lies in the first stage of the transformation, an intermediate formation of 6-imino-2,7-dioxabicyclo[3.2.1]octane-4,4,5-tricarbonitriles **3** as a result of interaction between 4-oxoalkane-1,1,2,2-tetracarbonitriles **1** and aldehydes.[8] The reasons for the diastereoselectivity of this process were studied and described by us previously.[8b]

To verify that the pyrano[3,4-*c*]pyrroles **2** are formed via the intermediates 6-imino-2,7-dioxabicyclo[3.2.1]octane-4,4,5-tricarbonitriles **3**, the synthesis of pyrano[3,4-*c*]pyrroles **2a−n** was implemented by heating the previously prepared bicyclo-[3.2.1]octanes **3a−n** in glacial acetic acid (Table 1).

**Table 1. Stepwise Synthesis of Densely Functionalized Pyrano[3,4-*c*]pyrrole Derivatives 2**

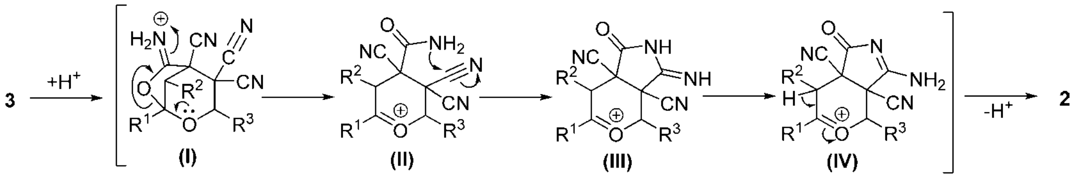


| entry | $R^1$ | $R^2$ | $R^3$ | 2 | yield (%)[a] |
|---|---|---|---|---|---|
| 1 | Me | Me | $C_6H_5$ | **2a** | 59 |
| 2 | $(CH_2)_4$ | | H | **2b** | 64 |
| 3 | $(CH_2)_4$ | | Me | **2c** | 77 |
| 4 | $(CH_2)_4$ | | *i*-Bu | **2d** | 75 |
| 5 | $(CH_2)_4$ | | Cy | **2e** | 71 |
| 6 | $(CH_2)_4$ | | $C_6H_5$ | **2f** | 84 |
| 7 | $(CH_2)_4$ | | 3,4,5-tri-MeO-$C_6H_2$ | **2g** | 80 |
| 8 | $(CH_2)_4$ | | 3-HO-4-MeO-$C_6H_3$ | **2h** | 77 |
| 9 | $(CH_2)_2CH$[*tert*-Bu]$CH_2$ | | $C_6H_5$ | **2i** | 69 |
| 10 | $(CH_2)_5$ | | $C_6H_5$ | **2j** | 75 |
| 11 | $C_6H_5$ | Me | $C_6H_5$ | **2k** | 73 |
| 12 | 4-Cl-$C_6H_4$ | Me | *i*-Pr | **2l** | 79 |
| 13 | 4-Cl-$C_6H_4$ | Me | $C_6H_5$ | **2m** | 75 |
| 14 | Me | 4-MeO-$C_6H_4$ | $C_6H_5$ | **2n** | 71 |

[a] Yields are given for the conversion of **3a−n** to **2a−n**.

On the basis of the described experimental observation, a plausible mechanism of pyrano[3,4-*c*]pyrroles **2** formation is depicted in Scheme 3. Bicyclo[3.2.1]octanes **3** have been protonated in an iminolactone moiety before electron density redistribution leads to the decyclization of the five-membered ring and the formation of a carbamoyl pyrylium resonance stabilized intermediate (**II**). Further intramolecular cyclization of spatially proximate carboxamide and the cyano group and deprotonation complete the formation of pyrano[3,4-*c*]pyrrole derivatives **2**.

**Scheme 3. Plausible Reaction Mechanism for the Cascade Assembly of Pyrano[3,4-*c*]pyrrole Derivatives 2**



It is important to note that we were accidentally able to isolate a trace amount of pyran-4-carboxamide **4** and to establish its structure by the X-ray diffraction analysis (Figure 3), but we could not repeat this procedure and characterize the compound by other spectra. Apparently, compound **4** corresponds to the deprotonated intermediate (**II**) (Scheme 3) and it is very inclined to intramolecular heterocyclization of the spatially proximate cyano and carboxamide group. This fact supports the proposed mechanism for pyrano[3,4-*c*]pyrroles **2** formation.

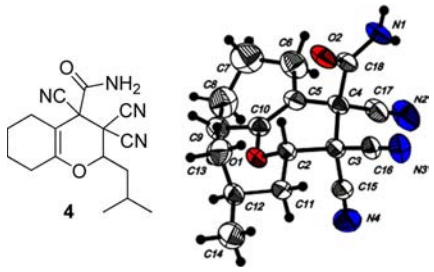
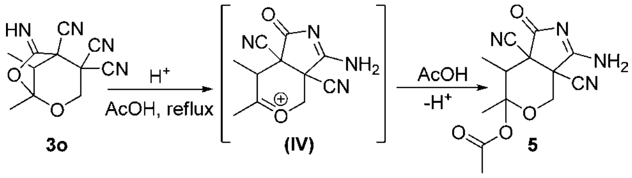


**Figure 3.** X-ray crystal structure of **4**.

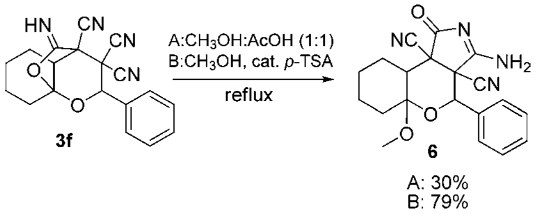
The proposed sequence of transformations is also consistent with an isolation of acetoxy pyrano[3,4-*c*]pyrrole derivative **5** after the heating of dioxabicyclo[3.2.1]octane **3o** in glacial acetic acid (Scheme 4). The reason for the formation of this derivative, probably, is the absence of steric hindrances and bulky substituents $R^1$ and $R^3$ in the carbenium-oxonium ion (**IV**) for the addition of acetic acid.

**Scheme 4. Synthesis of Acetoxy Derivative of Pyrano[3,4-*c*]pyrrole 5**



Also, to further support the proposed mechanism, we used methanol as a more nucleophilic cosolvent in the synthesis. In this case, the methoxy derivative of pyrano[3,4-*c*]pyrrole **6** was isolated (Scheme 5). It should be noted that the best yield and reaction rate were observed when methanol was used as the only solvent and the interaction was catalyzed with a few crystals of *p*-TSA. The formation of compounds **6** is diastereoselective, despite the presence of five asymmetric centers.

**Scheme 5. Synthesis of Methoxy Derivatives of Pyrano[3,4-*c*]pyrrole 6**



The formation of pyrano[3,4-*c*]pyrroles **6** with such a position of the methoxy group is convincing evidence of intermediate formation of a carbenium-oxonium ion (**IV**) during the pyrano[3,4-*c*]pyrroles **2** synthesis (Scheme 3). Moreover, the *cis*-position of the methoxy group and pyrrole moiety, relatively to the pyran ring (Figure 4), excludes the possibility of decyclization of the iminolactone ring by the nucleophilic attack of methanol (Scheme 6) and supports the proposed sequence of transformations in Scheme 3. At the same time, the formation of only one diastereomer with the axial methoxy group is apparently due to the anomeric effect, characteristic of α-hydroxypyran.[9]

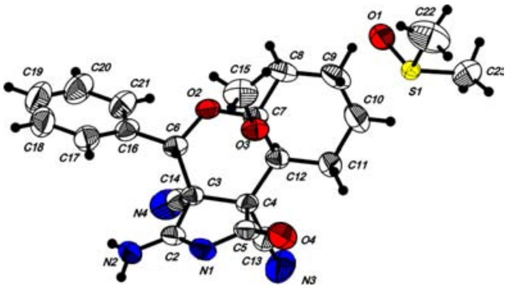
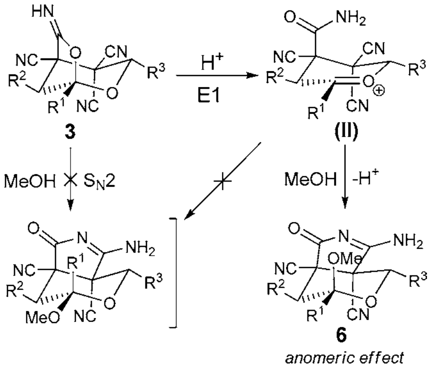


**Figure 4.** X-ray crystal structure of **6**.

**Scheme 6. Proposed Iminolactone Decyclization Mechanism**



Based on the described potential practical significance of functionalized pyrano[3,4-*c*]pyrroles, we decided to simplify the process for their preparation, bringing it to the simpler precursors. It is known that starting 4-oxoalkane-1,1,2,2-tetracarbonitriles were obtained as a result of acid-catalyzed interaction between TCNE and ketones.[10] According to this, we attempted to simplify the synthesis of pyrano[3,4-*c*]pyrroles **2** using a three-component reaction TCNE−ketone−aldehyde in the acetic acid. However, this approach did not lead to reproducible results. In most cases, the mixture became dark and oily while refluxing, and we could not yield any individual compounds from it. Without heating, the reaction required a significantly long reaction time and led to only trace amounts of target pyrano[3,4-*c*]pyrroles **2**.

As we expected, this multicomponent reaction is complicated by two main factors: the use of aromatic aldehydes can be accompanied by formation of their π-complexes with TCNE,[11] hindering further transformations; and α-unsubstituted aldehydes themselves can interact with TCNE and lead to the previously described derivatives.[10b] Therefore, we can affirm that synthesis of pyrano[3,4-*c*]pyrrole derivatives **2** is the most

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sufficient starting from the preliminarily prepared appropriate 4-oxoalkane-1,1,2,2-tetracarbonitrile **1** and aldehyde. Moreover, we noted that the total yield of pyrano[3,4-*c*]pyrrole derivatives **2** is bigger for the stepwise synthesis in most cases. For instance, the yield for the one-stage synthesis of pyrano[3,4-*c*]pyrrole **2c** is 52% (Scheme 1), while stepwise synthesis gives 75% (the yield of intermediate **3c** is 98%;[8a] further transformation gives the product **2c** in 77% yield). At the same time it should be noted that for compound **2o** the yield is 87%, and we could not isolate the corresponding intermediate dioxabicyclo[3.2.1]octane.

In conclusion, we have developed a new convenient approach to the synthesis of densely functionalized pyrano-[3,4-*c*]pyrrole derivatives with sufficient yields and an exceptional diastereoselectivity. It is important to note that a double heteroannulation occurred in the course of the transformations. The process of such a tandem construction of two heterocycles is the basis of so-called ≪DHARMA≫ synthesis that we have developed.[12] Further this transformation is the new important branch in the investigation of Diversity-Oriented Synthesis (DOS) based on 4-oxoalkane-1,1,2,2-tetracarbonitriles.[7] Moreover, the representatives of intermediate 6-imino-2,7-dioxabicyclo[3.2.1]octane-4,4,5-tricarbonitriles **3** have demonstrated cytotoxic activity in various cancer cell lines;[13] therefore, the derived pyrano[3,4-*c*]pyrroles **2** is very promising for further biological studies.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00867.

Experimental procedures, product characterization, crystallographic data, and $^1$H and $^{13}$C NMR spectra (PDF)
X-ray crystallographic data for **2f** (CIF)
X-ray crystallographic data for **4** (CIF)
X-ray crystallographic data for **6** (CIF)

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### Notes

The authors declare no competing financial interest.

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(14) The crystallographic data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. The CCDC numbers are 1470437 (**2f**), 1470436 (**4**), and 1470435 (**6**).