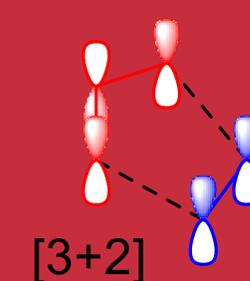




# 1,3-DIPOLAR CYCLOADDITION REACTION OF FUSED 1H-PYRROLE-2,3-DIONES WITH NITRONES: A DIVERGENT APPROACH TO PYRROLOISOXAZOLES\*

Ekaterina E. Khramtsova (Stepanova), A. N. Maslivets

Perm State University,  
614990, Russia, Perm, ul. Bukireva, 15,  
caterina.stepanova@psu.ru; +7 (902) 79 25 170; koh2@psu.ru

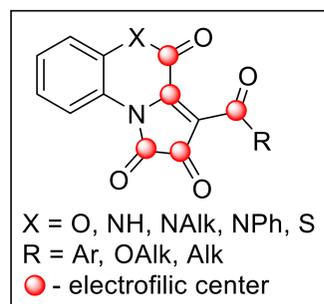


Divergent synthesis is a promising trend in small molecules drug discovery. It allows to investigate the chemical space more efficiently and economically since diverse compounds collections are created from a limited set of reagents.

1,3-Dipolar cycloaddition is a facile tool for simultaneous introduction of several stereogenic centers through a single step to afford complex heterocyclic structures. In the view of requirements of green chemistry, it seems to be a beneficial synthetic approach since it proceeds in a PASE manner along with high regio- and stereoselectivity.

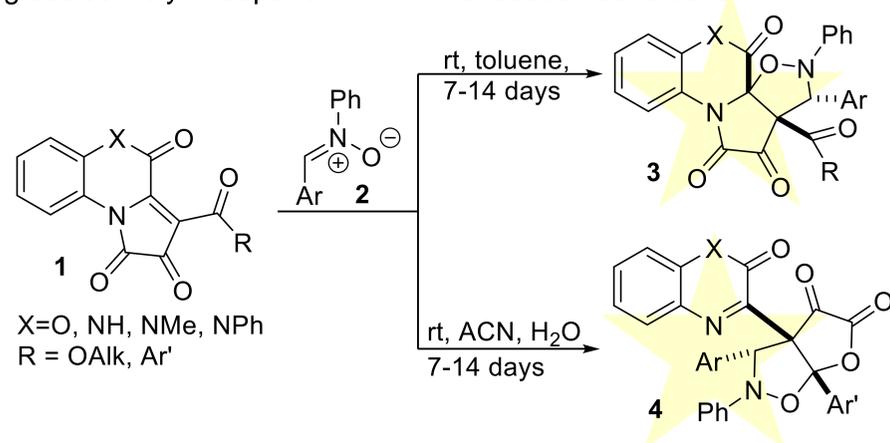
1*H*-Pyrrole-2,3-diones fused at [e]-side (hetareno[e]pyrrole-2,3-diones (HPDs)) are readily available polyelectrophilic reagents enabling synthesis of various heterocyclic systems with divergent skeletons.

hetareno[e]pyrrole-2,3-diones **1**



X = O, NH, NAlk, NPh, S  
R = Ar, OAlk, Alk  
● - electrophilic center

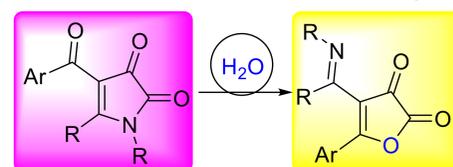
We have developed a divergent approach to skeletally diverse isoxazoles *via* 1,3-dipolar cycloaddition reaction of HPDs **1** with nitrones **2**. Isoxazoles **3** and **4** can be obtained from a single set of reagents (compounds **1** and **2**), and the formation of compounds **3** or **4** proceeds regioselectively in dependence on the reaction conditions.



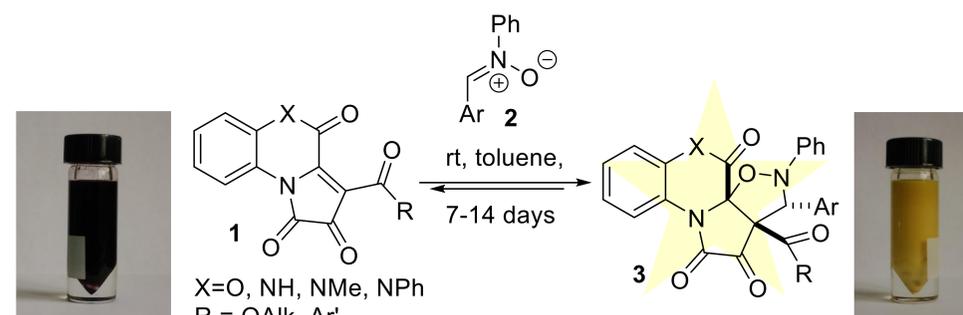
X=O, NH, NMe, NPh  
R = OAlk, Ar'

The source of skeletal diversity of the developed approach is an unprecedented water-mediated 1*H*-pyrrole-2,3-dione–furan-2,3-dione rearrangement.

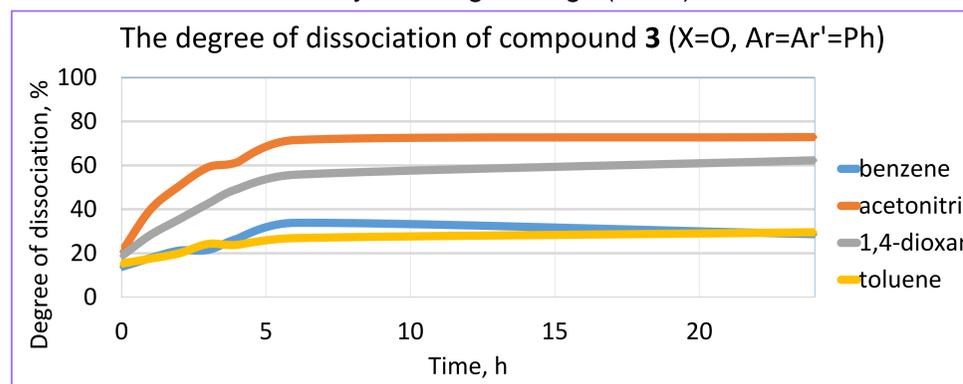
water-mediated  
pyrrole-2,3-dione - furan-2,3-dione rearrangement



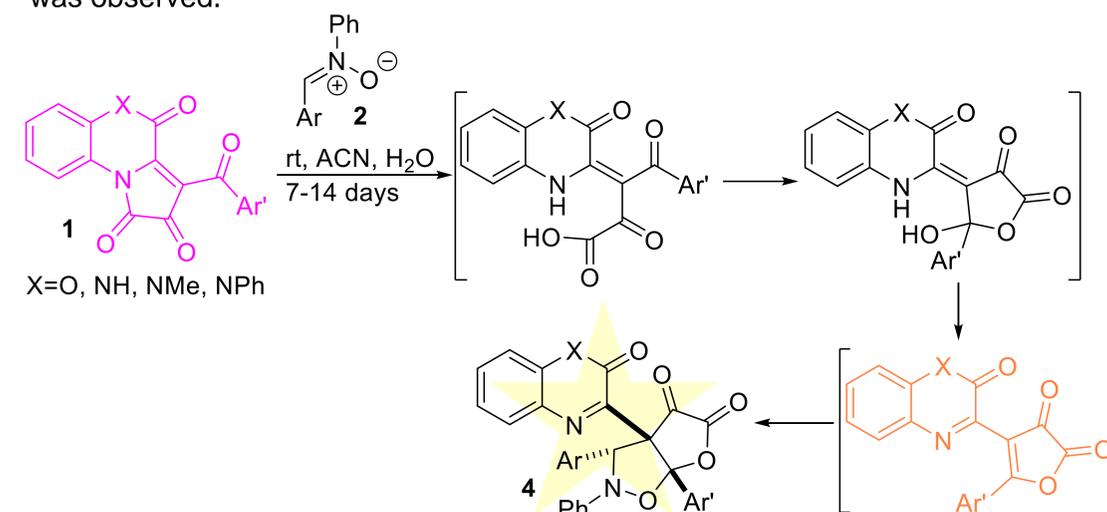
Tetracyclic fused isoxazoles **3** were formed in the result of reaction of HPDs **1** with nitrones **2** under anhydrous conditions. The reaction progress was monitored by the change of color of the reaction mixture.



Formation of compounds **3** was found to be reversible. The degree of dissociation of compounds **3** depended on the solvent's polarity. Polar solvents facilitated their dissociation. In addition, the degree of dissociation was found to be dependent on R-substituent; alkoxy carbonyl bearing compounds **3** (R=OAlk) were found to be more stable to dissociation than their aroyl-bearing analogs (R=Ar).



Bicyclic fused isoxazoles **4** were formed in the result of reaction of HPDs **1** with nitrones **2** under aqueous conditions. The reaction progress was monitored by UPLC-UV-MS. No dissociation of compounds **4** during the storage of their solutions was observed.



Aroyl bearing (R=Ar) compounds **3** and **4** were formed diastereoselectively with exclusive formation of *endo*-diastereoisomers. For alkoxy carbonyl bearing compounds **3** (R=OAlk), formation of *exo*- and *endo*-diastereoisomers was observed, and besides *exo*-diastereoisomers were converted to *endo*-ones when stored as solutions.

Structures of compounds **3** (R=Ar, OAlk (*endo* and *exo*)) and **4** were unequivocally proved by single crystal X-ray diffractometry.



Department of chemistry of PSU.

Special Issue "Cycloaddition Reaction in Organic Synthesis" in a New MDPI Open Access Journal: Organics ----->



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