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A novel approach to biologically relevant oxazolo[5,4-*d*]pyrimidine-5,7-diones *via* readily available diazobarbituric acid derivatives

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ABSTRACT

An alternative route from 1,3-disubstituted barbituric acids to biologically relevant oxazolo[5,4-*d*]pyrimidine-5,7-diones was developed that features sulfonyl-azide-free (SAFE) diazo transfer and $Rh_2(esp)_2$-catalyzed cycloaddition of the resulting 5-diazobarbituric acids with aliphatic and aromatic nitriles. Besides being shorter compared to the previously described approaches, the method allows introduction of alkyl substituents at the 1,3-oxazole ring of the fused heterocyclic system.

The pyrimidine-2,4-dione core is typically introduced into more complex heterocyclic frameworks *via* the use of barbituric acid and its derivatives as building blocks. The latter have been utilized in the design and synthesis of diverse types of heterocyclic and carbocyclic compounds [1]. Besides the prominence of barbiturates as central nervous system drugs [2], fused polycyclic pyrimidine-2,4-diones can be regarded as privileged motifs [3], considering the diversity of biological activities displayed by such compounds. One such chemotype, oxazolo[5,4-*d*]pyrimidine-5,7-diones, has recently attracted our attention. It is featured in biologically active compounds such as FGFR1 inhibitor **1** for cancer treatment [4], metalloproteinase inhibitor **2** for the treatment of arthritis, inflammation and cancer [5], adenosine receptor antagonist **3** to treat neurodegenerative disease [6] and Syngenta's pesticide series represented by compound **4** (Fig. 1) [7].

The currently described strategies to assemble oxazolo[5,4-*d*]pyrimidine-5,7-diones are rather limited and rely on 5-aminopyrimidine-2,4,6-trione **5** prepared, in turn, over two steps (nitrosation followed by nitroso group reduction) from barbituric acid derivatives **6**. In the most exploited approach [4,8–10], amine **5** is first condensed with aromatic aldehydes and the respective intermediate imines are cyclodehydrated with $SOCl_2$ [4,8,9] or *N*-bromosuccinimide [10] to give the target compounds (**7**). Alternatively, the latter can be formed by heating amine **5** in aroyl chlorides as a solvent [11] (Scheme 1). One isolated report [12] described the synthesis of **7** by direct condensation of 5-nitroso-1,3-dimethylbarbituric acid with various Wittig phosphonium ylides; however, subsequent research in the area has not utilized this methodology and the approach depicted in Scheme 1 currently remains the principal means to synthesize oxazolo[5,4-*d*]pyrimidine-5,7-diones **7**. The following drawbacks of this synthesis are apparent: it is multistep and the R′ substituent diversity is limited to (hetero)aryl groups.

Our recent experience preparing heterocycle-fused oxazoles from heterocyclic α-diazocarbonyl compounds [13] *via* Rh(II)-catalyzed [2+3]-cycloaddition with nitriles prompted us to consider an alternative disconnection of scaffold **7**. We reasoned that the oxazole ring could be obtained from a similar coupling of nitriles (R′CN) with metal carbenes derived from 5-diazobarbituric acids **8**. The latter were introduced as early as 1952 [14] and have been shown to undergo selected transformations which are typical of α-diazocarbonyl compounds. In particular, Rh(II)-catalyzed OH-insertion, [15] C_{Ar}-H insertion, [16] dichlorination reactions [17] and [2+3]-cycloadditions with styrenes and arylacetylenes [18] have been reported, thus making 5-diazobarbituric acids versatile building blocks (Fig. 2). Thus, we decided to investigate 5-diazobarbituric acids **8** in the Rh^{II}-catalyzed cycloaddition with nitriles, which would constitute a simpler and more flexible entry into oxazolo[5,4-*d*]pyrimidine-5,7-diones **7** compared to previously reported approaches. Herein, we present the results of these studies.

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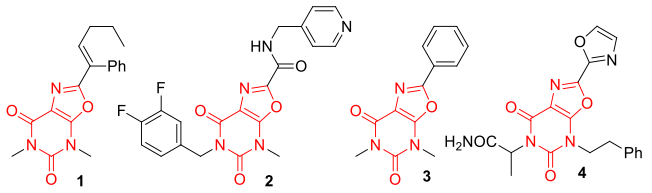
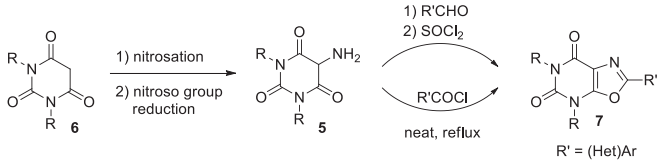


Fig. 1. Examples of biologically active compounds containing the oxazolo[5,4-*d*]pyrimidine-5,7-dione core.



Scheme 1. Typical approaches to oxazolo[5,4-*d*]pyrimidine-5,7-diones reported in the literature.

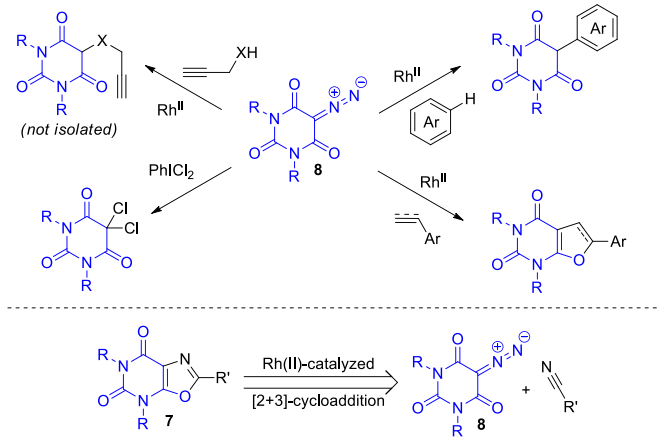
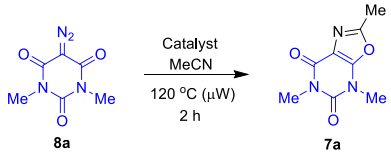


Fig. 2. Examples of reactions described for 5-diazobarbituric acids **8** in the literature [15–18] and the approach investigated in this work.

Table 1
Condition screening for the cycloaddition of **8a** and acetonitrile.



8a **7a**

Entry	Catalyst	Amount (mol%)	Yield **7a** (%)[a]
1	$Rh_2(OAc)_4$	1	65
2	$Rh_2(Oct)_4$	1	34
3	$Rh_2(C_4F_7O_2)_4$	1	Trace[b]
4	$Rh_2(esp)_2$	1	86
5	$Rh_2(esp)_2$	1	82[c]
6	$Rh_2(Piv)_4$	1	78
7	$Rh_2(CF_3CO_2)_4$	1	47
8	$BF_3{\cdot}Et_2O$	100	Trace[b]
9	AgOTf	10	Trace[b]

[a] Isolated yield.
[b] according to TLC analysis of the reaction mixture.
[c] reaction was carried out at 130 °C under conventional heating for 3 h.

Utilizing the previously developed conditions for the Rh^{II}-catalyzed [2+3]-cycloaddition of α-diazo homophthalimides [13], we screened a number of transition metal catalysts and $BF_3{\cdot}OEt_2$ as representative Lewis acid (Table 1). The best result (86% yield) was obtained in the $Rh_2(esp)_2$-catalyzed reaction between 1,3-dimethyl-5-diazobarbituric acid (**8a**) and acetonitrile conducted at 120 °C under microwave irradiation over 2 h (Entry 4). While shortening the 120 °C reaction time to 1 h under microwave irradiation led to incomplete conversion, slightly increasing the reaction temperature (130 °C) and time (3 h) resulted in full conversion and a comparable yield (82%) under conventional heating (Entry 5), thus making the newly discovered transformation amenable to both modes of activation.

Having identified the optimal conditions for the synthesis of oxazolo[5,4-*d*]pyrimidine-5,7-diones, we proceeded to investigate its scope using a set of 5-diazobarbituric acids **8a–f** (Fig. 3) conveniently prepared from their 5-unsubstituted counterparts by the recently developed sulfonyl-azide-free (SAFE) diazo transfer protocol [19].

The results of these experiments are presented in Scheme 2. The formation of target oxazolo[5,4-*d*]pyrimidine-5,7-diones **7** was efficient in the case of symmetrically 1,3-disubstituted diazo cores **8a–c** and **8f** and proceeded well under conventional heating or microwave irradiation with aliphatic and aromatic nitriles while tolerating labile haloalkyl groups (albeit with diminished yields, *cf.* **7e–f**). Non-symmetric 5-diazobarbituric acid **8d** reacted primarily at the more 'enolizable' carbonyl to give **7j** as the major product. Its identity (as well as that of its regioisomer **7j′**) was established by HMBC correlations (Fig. 4). Monosubstituted 5-diazobarbituric acid **8e** failed to give the desired 1,3-oxazole product **7 l**.

Attempts to transfer the [2+3]-cycloadditions described herein to diazo Meldrum's acid **9** gave a curious result. While the reaction gave full conversion and good isolable yield of a product, its structure was assigned to 2,5-dimethyl-7*H*-oxazolo[4,5-*e*] [1,3]oxazin-7-one (**10**) rather than the expected adduct **11**. Considering that the reaction was conducted under prolonged microwave irradiation in acetonitrile as a solvent, it is realistic to expect product **10** to arise from a known [20] elimination of an acetone molecule, formation of acyl ketene **12** and Diels-Alder-like cyclocondensation [21] of the latter with another molecule of acetonitrile (Scheme 3).

In summary, we have developed a novel approach to biologically relevant oxazolo[5,4-*d*]pyrimidine-5,7-diones. It relies on the convenient synthesis of 5-diazobarbituric acids by *SAFE* diazotransfer and $Rh_2(esp)_2$-catalyzed cycloaddition with nitriles conveniently conducted under conventional heating or microwave irradiation. Besides the practical convenience, the synthesis affords greater diversity of substituents on the 1,3-oxazole ring compared to the previous cyclodehydration-based methods which work only for (hetero)aryl-substituted substrates.

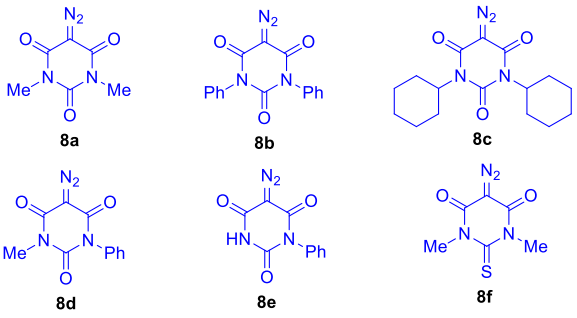
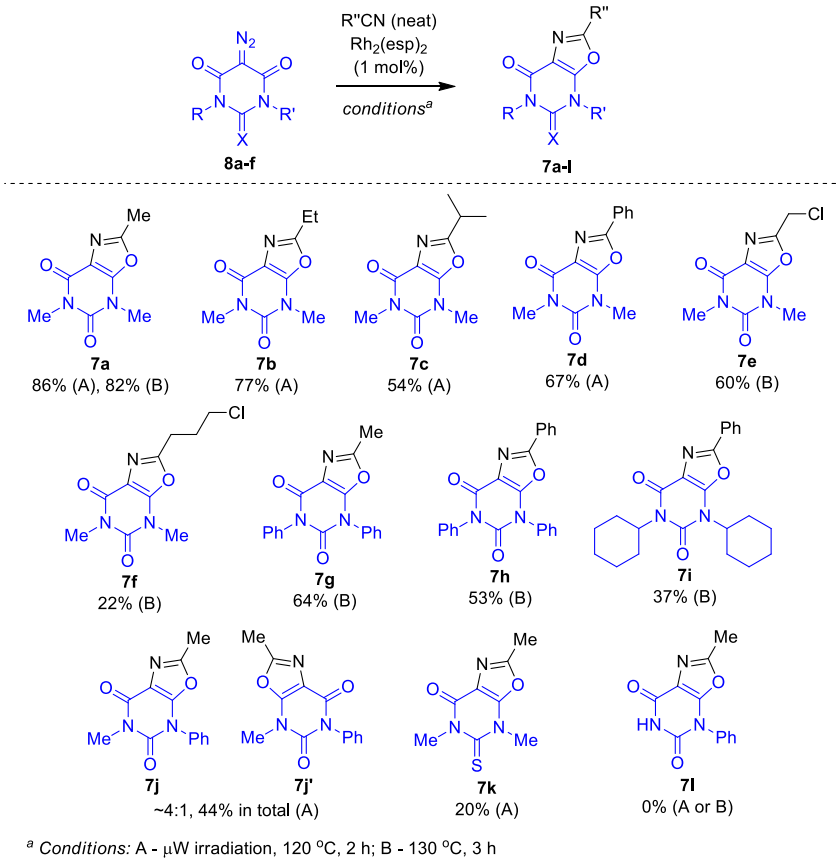


Fig. 3. 5-Diazobarbituric acids **8** employed in this study.



Scheme 2. Preparation of oxazolo[5,4-*d*]pyrimidine-5,7-diones **7a–l**.

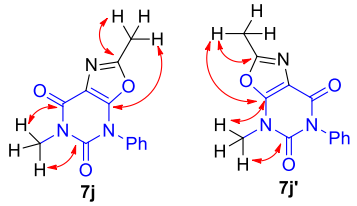
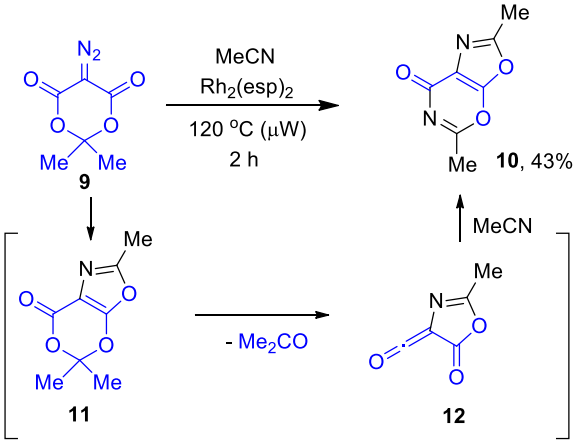


Fig. 4. HMBC correlations permitting the distinction between **7j** and **7j'** regioisomers.



Scheme 3. Attempted reaction with diazo Meldrum's acid (**9**).

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2019.151120.

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