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Scaffold Hopping *via* a Transannular Rearrangement–Encompassing Cascade

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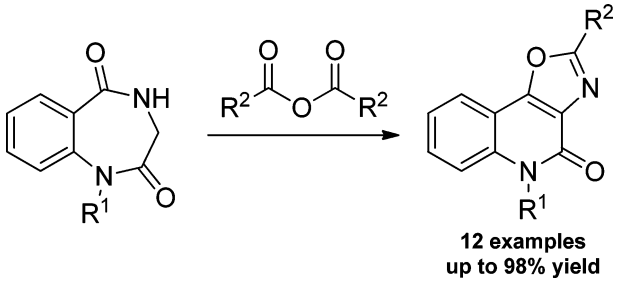
ABSTRACT



A novel reaction cascade for converting benzodiazepinediones into oxazoloquinolinones using carboxylic acid anhydrides in the presence of base has been developed using flow methods. Products are obtained in yields up to 98%.

In the course of previous work in our group dealing with the construction of (hetero) benzodiazepinediones (BDPs),[1] two different compounds were unexpectedly isolated when treating **3** with acetic anhydride (Scheme 1). Based on the work of Pigeon and co-workers,[2] we were expecting the *in situ* generated open-chain precursor **3** to undergo ring closure in the presence of acetic anhydride and K_2CO_3, yielding its corresponding BDP. Imide **4a** and compound **5a** were obtained instead from the reaction. Furthermore, imide **4a**, when brought back under the same reaction conditions, gave rise to compound **5a**, indicating its intermediacy in a yet unreported cascade reaction. Not only the supposed cascade reaction but also the compound obtained (**5a**) caught our attention, as this scaffold is brought into relation with numerous biological activities, including Gly/NMDA receptor antagonism,[3] modulating GABA receptor inverse agonism,[4] and inhibition of multidrug resistance-associated protein 1 (MRP1).[5]

The literature hinted toward a plausible mechanism for the observed cascade reaction:[2,6−10] first, we assume that BDP **6**, our original compound of interest, is indeed being formed during the reaction (Scheme 2). Subsequent acylation of **6** yields the isolated imide **4**. Comparable cyclic imides (activated lactams) are known to undergo a transannular rearrangement[6−9] reaction under basic conditions, giving rise to acylated α-amino ketones **9**.

Finally, compounds **9** are cyclodehydrated in a Robinson–Gabriel type reaction[10] by the excess of carboxylic acid anhydride present, yielding oxazoloquinolinones (OQOs) **5**.

As this cascade reaction is most likely taking place *via* a BDP intermediate **6**, and also the synthesis of these classical 'privileged scaffolds' has already been investigated extensively,[11] we decided to use BDPs as starting compounds in our further optimization of the *Transannular Rearrangement of an Activated Lactam Encompassing Cascade* (TRALEC) reaction for the synthesis of OQOs.

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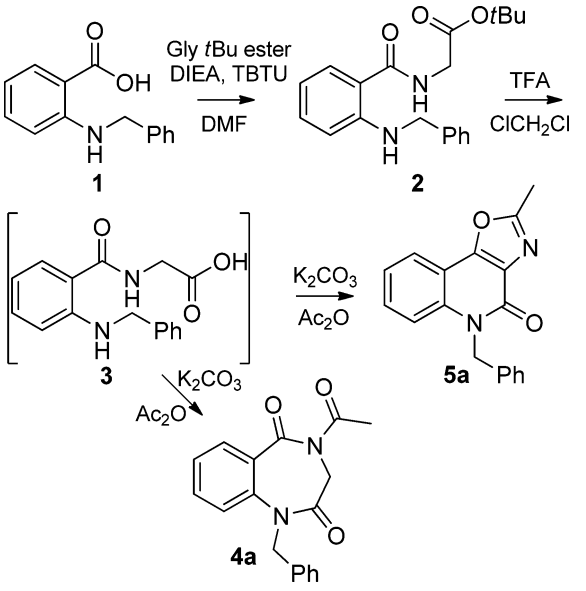
Scheme 1. Conversion of 2-Aminobenzoic Derivative **1**



The N_1-functionalized BDP starting materials were conveniently prepared from isatoic anhydride using a two-step procedure (Scheme 3). First, a [4 + 3] cyclocondensation reaction of isatoic anhydride **11** with glycine was conducted in DMSO, largely following the procedure as described by Clark and co-workers.[12] In the second step unsubstituted BDP **12** was selectively alkylated on the N_1-position, using a procedure based on the reaction protocol used by Cheng and co-workers.[13] DMSO was used as solvent in this series of alkylation reactions, as to our knowledge it is the only common solvent in which BDP **12** dissolves sufficiently. Apart from the reaction in which benzyl bromide was used as an alkylating reagent, N_1-functionalized BDPs **6** were generally obtained in fair yields. Indeed, benzyl bromide is known to undergo side reactions with DMSO.[14]

Optimization of the TRALEC reaction which converts BDPs **6** to OQOs **5** (Scheme 4) started with the previously applied reaction protocol, originally intended to convert an open-chain precursor **3** to its corresponding BDP. BDP **6** and 3 equiv of K_2CO_3 were added to acetic anhydride (solvent), which, after being stirred for 30 min at room temperature, was refluxed for 24 h. Unfortunately, we were facing two considerable problems while exploring aforementioned reaction conditions. First, acceptable conversions (> 40%) were never achieved, and second, persistent side reactions were observed giving rise to unidentified side products of which the share increased linearly with reaction time. We were to address both of these problems in a systematic way.

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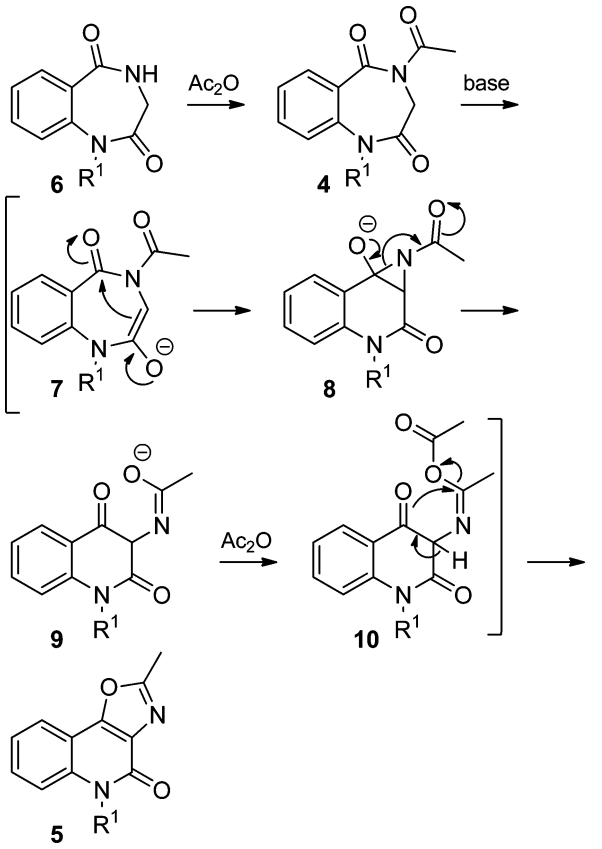
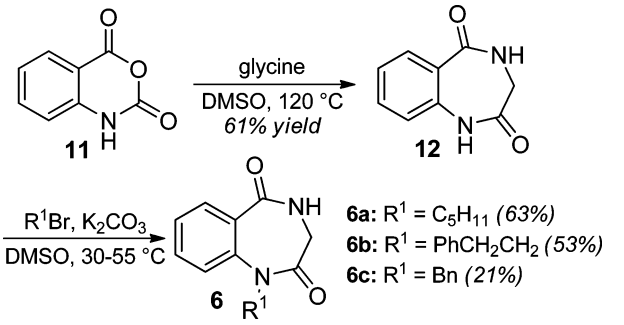
Scheme 2. Mechanism Proposed for the Formation of **5**

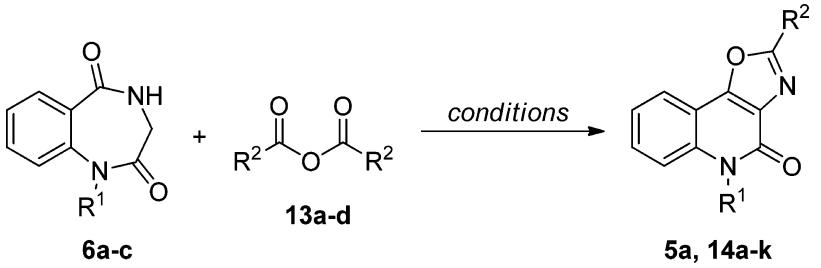


Scheme 3. Preparation of BDPs **6**



To reduce the share of side reactions, first the reaction mixture itself was modified. As we believed that the large excess of acetic anhydride was mainly responsible for these side reactions, a logical first adjustment was to reduce the amount of acetic anhydride in the reaction. Although stoichiometrically only 2 equiv of acetic anhydride are required in the reaction cascade (Scheme 2), we decided still to use 10 equiv to ensure proper conversion of the BDP starting material. *o*-Xylene was chosen as a suitable solvent in which the reaction can be carried out, as it is known as both a high boiling and a relatively inert solvent. Also, to avoid excessive gas evolution, the K_2CO_3 base was

Table 1. Synthesis of OQOs from BDPs **6** and Carboxylic Acid Anhydrides **13**[a]

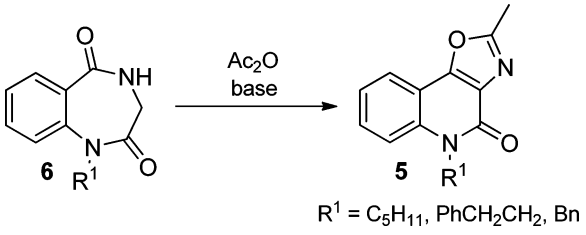


OQO	R^1	R^2	reactor conditions	yield (%)[b]
14a	C_5H_{11}	Me	300 °C, 200 μL/min[c]	94
14b	C_5H_{11}	*n*Pr	300 °C, 200 μL/min[c]	98
14c	C_5H_{11}	*i*Pr	300 °C, 200 μL/min[c]	94
14d	C_5H_{11}	Ph	300 °C, 200 μL/min[c]	69
14e	$PhCH_2CH_2$	Me	300 °C, 100 μL/min[d]	83
14f	$PhCH_2CH_2$	*n*Pr	300 °C, 100 μL/min[d]	87
14g	$PhCH_2CH_2$	*i*Pr	300 °C, 100 μL/min[d]	86
14h	$PhCH_2CH_2$	Ph	220 °C, 400 μL/min[e]	69
5a	Bn	Me	220 °C, 400 μL/min[e]	69
14i	Bn	*n*Pr	220 °C, 400 μL/min[e]	79
14j	Bn	*i*Pr	220 °C, 400 μL/min[e]	79
14k	Bn	Ph	220 °C, 400 μL/min[e]	64

[a] Reagents and conditions: BDP **6** (60 mg), anhydride **13** (10 equiv), DBU (5 equiv), *o*-xylene (5 mL), gently heated until complete dissolution of reagents. The residence time in the flow reactor was 2 min. [b] Isolated yield after workup and silica gel chromatography. [c] Reactor 1: length (2 m), diameter (0.51 mm). [d] Reactor 2: length (1 m), diameter (0.51 mm). [e] Reactor 3: length (1 m), diameter (1.02 mm).

substituted for potassium acetate, as this base is generated *in situ* from acetic anhydride during previous reactions. Implementation of this modified reaction protocol showed that indeed the amount of side reactions was strikingly reduced. However, similar conversions were observed as before.

Scheme 4. Exploration of the TRALEC Reaction on BDPs **6**



As in conventional batch approaches the reaction temperature is usually limited by the boiling point of the solvent, the focus of our research shifted toward more efficient heating techniques to obtain higher conversions. In our reaction cascade, the key transannular rearrangement was also found to be the rate-determining step (RDS). Indeed, after reaction, imides **4** were always found in the reaction mixture while compounds **9** were not (Scheme 2), indicating that both acylation of BDP **6** and cyclodehydration of compound **9** to OQO **5** proceed faster than the transannular rearrangement reaction. Also, the poor conversions observed in previous experiments indicate that the RDS involves a considerably high activation energy, thus making efficient heating of the reaction again required to counteract side reactions (see Supporting Information). The development of a microwave-assisted reaction protocol was not undertaken because of specialized experimental equipment demands for upscaling, although several authors show this approach is actually feasible.[15−17]

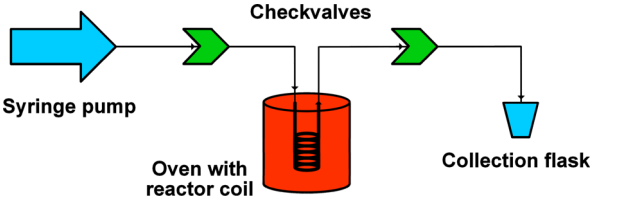


Figure 1. Schematic overview of experimental flow setup.

On the other hand it was continuous flow chemistry in particular that caught our attention. Flow technology not only allow us to exceed the boiling point of the reaction

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solvent but also allows short retention times, avoiding prolonged heating of the reaction mixture.

For this purpose, a flow reactor was built in-house from commercially available stainless steel HPLC tubing. The reactor coil is heated by means of an HPLC column oven. A schematic overview of the experimental setup is depicted in Figure 1. Continuous flow chemistry, however, requires homogeneous reaction conditions, which made it crucial to identify an organic base that dissolves readily in the reaction mixture before injection. After a screening of different bases under batch conditions (see Supporting Information), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was found to be the suitable base, as it both catalyzes the TRALEC reaction and is soluble in the reaction mixture. Also, the concentration of reactants had to be lowered to ensure homogeneous conditions upon injection into the flow reactor. As OQOs **14a**, **14e**, and **5a** were isolated in yields varying from 69% to 94%, we were encouraged to also give alternative carboxylic acid anhydrides a try in the TRALEC reaction. Indeed, the utilization of (iso)butyric anhydride and benzoic anhydride analogously gave rise to the corresponding OQOs in yields varying from 64% to 98% (Table 1). These interesting results show that the TRALEC reaction might be implemented for the preparation of more complex OQO based scaffolds, as it introduces a conveniently adjustable point of diversity on the C_2-position of the OQO skeleton.

In conclusion, an efficient reaction protocol has been developed using a flow method for converting BDPs **6** to pharmaceutically interesting OQOs in the presence of a carboxylic acid anhydride **13** and base. Using this protocol, OQOs have been isolated in yields up to 98%. To extend the scope of the TRALEC reaction even more, in future work we are planning its implementation on other diazepine systems as well as alternative lactam systems, such as diketopiperazines.

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Supporting Information Available. Experimental procedures, characterization data, and copies of spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.