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Convenient access to novel functionalized pyrazino[1,2-*b*] isoquinolin-6-one and diazepino[1,2-*b*]isoquinolin-7-one scaffolds via the Cushman multicomponent reaction followed by post-condensation

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ABSTRACT

Post-multicomponent reaction modifications of Cushman reaction-derived 1,2,3,4-tetrahydroisoquinolin-4-carboxylic acids turned out to be a surprisingly underdeveloped strategy in scaffold-oriented synthesis. In this Letter, we describe a concise synthesis of hitherto unreported pyrazino- and diazepino-fused isoquinolones in two chemical operations. The synthesis involves the use, for the first time, of aryl glyoxals as carbonyl components for the Cushman multicomponent reaction.

Coupling a multicomponent reaction (MCR) with a premeditated post-MCR event, in a sequence, has proven itself as a rich and operationally simple source of new and diverse heterocyclic scaffolds. The power of this approach has been explored in detail, in particular, for isocyanide-based MCRs, such as the Ugi reaction.[1]

The condensation of Schiff bases with various cyclic anhydrides was initially discovered by Castagnoli and Cushman,[2] and subsequently extended to homophthalic anhydride at the start of Cushman's independent career (with a coincidental independent report from a Bulgarian group[3]). The latter reaction (which we would like to term the Cushman reaction) is essentially a three-component condensation of an amine and a carbonyl (most often, an aldehyde[4]) component with a homophthalic anhydride (**1**). It received particular prominence as a tool to generate various biologically active compounds based on the resulting 1,2,3,4-tetrahydro-1-oxo-isoquinolin-4-carboxylic acid (**2**) scaffold (Fig. 1).[5] The latter contains two stereogenic centers and can be obtained diastereoselectively as pure *cis*- or *trans*-isomer—or as a mixture of both—depending on the conditions of the condensation step.[6]

On reviewing the literature on the Cushman reaction, we were surprised at the scarcity of examples of post-MCR modifications coupled to this powerful and atom-efficient[7] three-component process. Not intending to undertake an exhaustive review of the literature, we would like to note the following examples (Fig. 2): (a) the unexpected formation of 5-benzo[*d*]naphtha[2,3-*b*]pyran **3** via a base-triggered rearrangement of cyanomethyl derivative **4**;[8] (b) elaboration of the natural (±)-corynoline core **5** via manipulation of judiciously crafted precursor **6**;[9] (c) formation of indenoisoquinolone **8** via Friedel–Crafts cyclization of **7** in PPA[10]—a transformation that ultimately led to the discovery of potent topoisomerase inhibitors[11] and retinoid X receptor (RXR) agonists (termed rexinoids);[12] (d) an intriguing oxidative conversion of indenoisoquinoline **8** into isoquinoline-3-spiro-3′-phthalide **9**;[13] (e) reductive manipulation of the carboxylic function of Cushman adduct **10** leading to the formation of cyclopropane-fused core **11** related to the duocarmycins;[14] (f) similar ester reduction with subsequent straightforward conversion of the resulting alcohols into amino-substituted compounds **12**;[15] (g) formation of the fused lactones **13** and **14** via intramolecular S_N2-type lactonization[16] or phenol acylation,[17] respectively.

Puzzled by this unfilled void in synthetic organic chemistry, and excited about the vast scaffold-oriented research opportunity, we proceeded to investigate the feasibility of various post-Cushman

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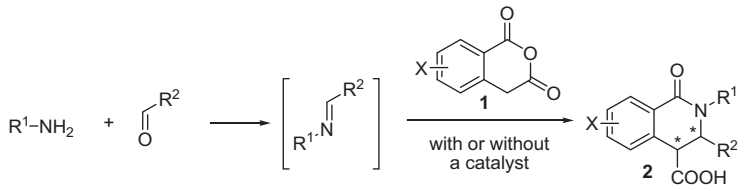

Figure 1. The Cushman reaction.

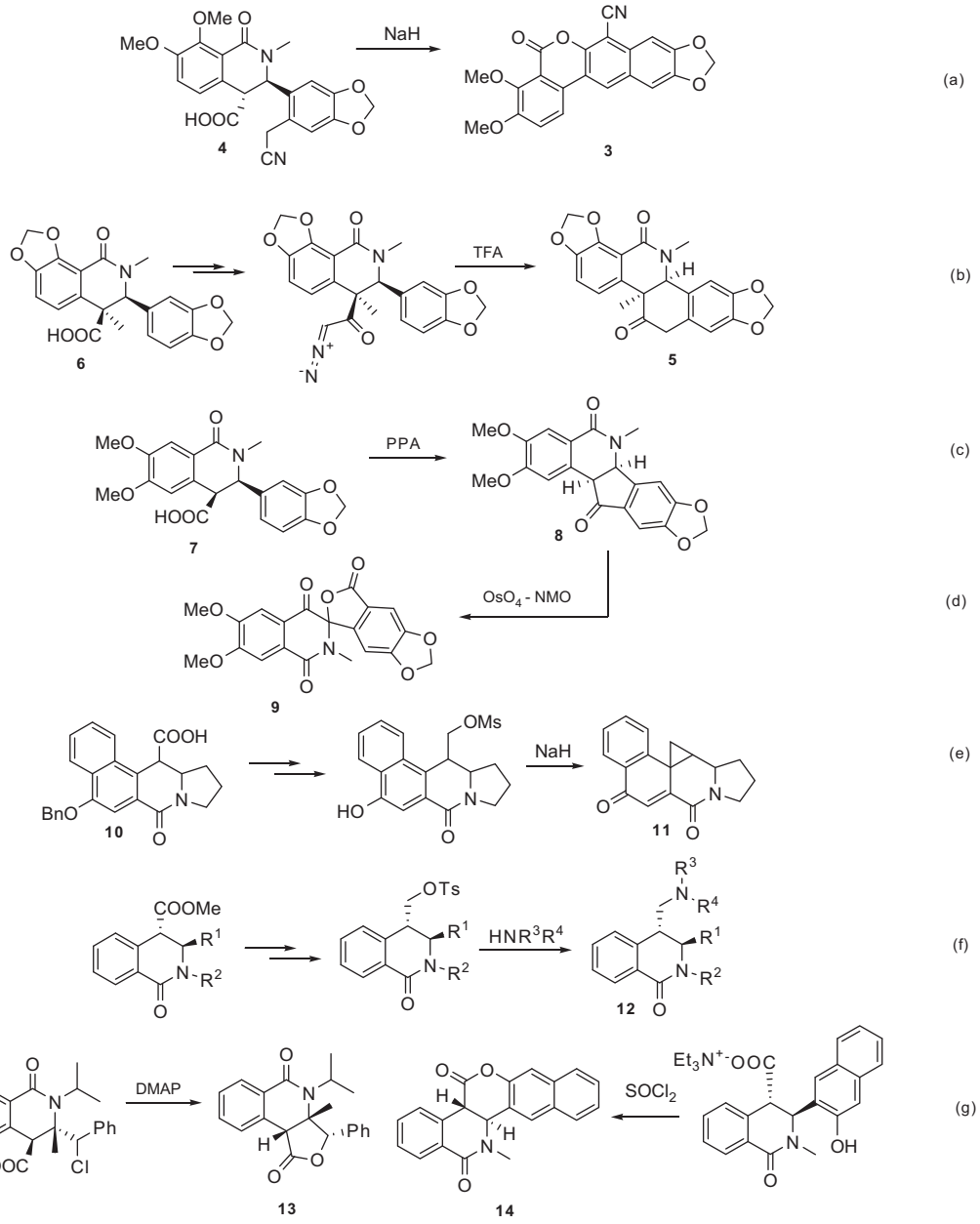

Figure 2. Examples of post-Cushman transformations described in the literature.

events as a means to build molecular complexity in a practically simple, expeditious manner. Herein, we report on our first findings in this area.

We reasoned that incorporating a masked amino functionality in one of the reagents for the Cushman reaction, and a relatively unreactive carbonyl functionality in the other would create an opportunity for a ring-forming process in the Cushman adduct once the amino function is unmasked. While there are a number of commercially available monoprotected diamines (such as *N*-Boc ethylenediamine or 1,3-diaminopropane), identifying an appropriate dicarbonyl input that would unequivocally react in the Cushman step, proved more challenging. After considering several possibilities (including monoprotected dicarbonyl variants), we focused on aryl glyoxals, which we expected to react