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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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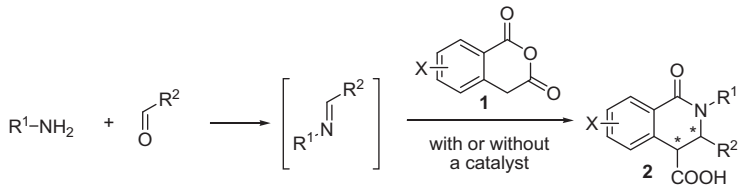


Figure 1. The Cushman reaction.

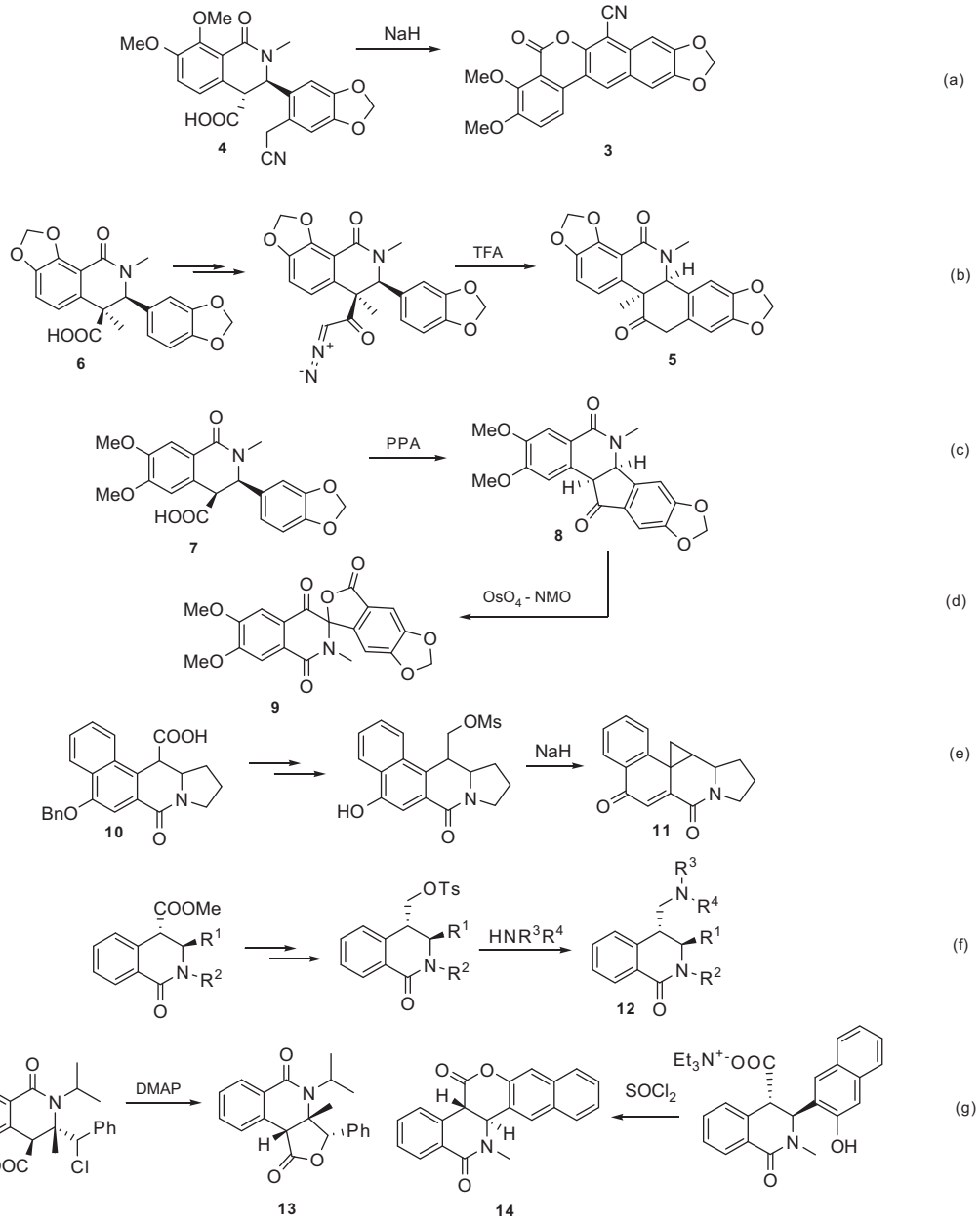
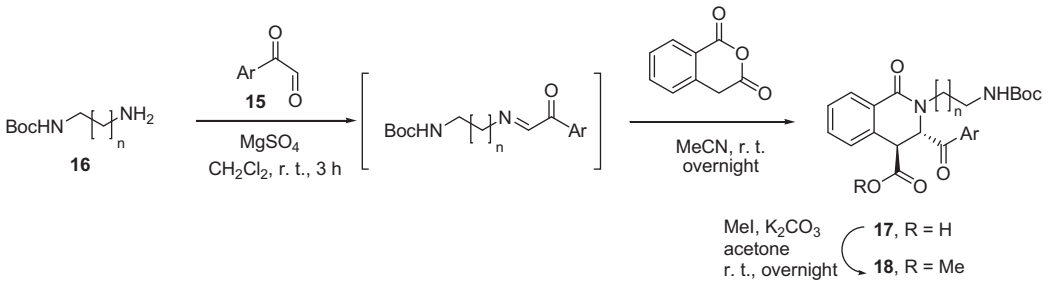


Figure 2. Examples of post-Cushman transformations described in the literature.

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



Scheme 1. The Cushman reaction of aryl glyoxals **15**.

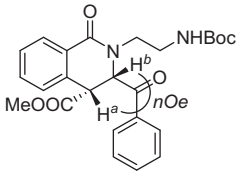


Figure 3. NOESY correlations observed in **18a** confirming the *cis* stereochemistry of the Cushman adducts.

chemoselectively at the aldehyde function leaving the aromatic ketone functionality available for subsequent interaction with the amino group, when the latter is unmasked.

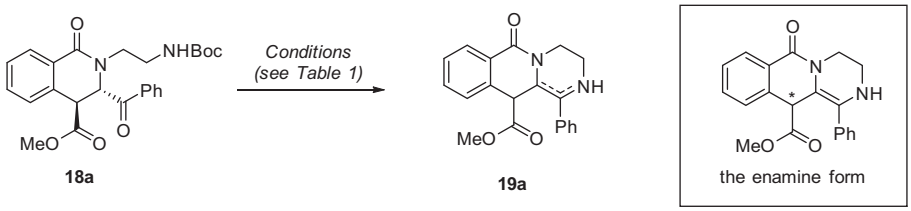
There were no examples of using glyoxals as carbonyl components for the Cushman reaction in the literature.[18] However, we found a range of substituted phenyl glyoxals **15** that reacted very efficiently—first with the amines **16** and then with homophthalic anhydride to give a single diastereomer of the acids **17a–o** (as established by the presence of only one set of product signals in the ^{1}H NMR spectrum of the crude reaction mixtures). For the sake of easier chromatographic purification, the crude carboxylic acids **17a–o** were esterified and the resulting methyl esters **18a–o** were isolated in good to excellent yields (from homophthalic anhydride) by column chromatography, and were fully characterized (Scheme 1, see also the Supporting information). The relative stereochemistry of the sole Cushman reaction-derived esters **18** was established as *cis*, according to the presence of a through-space interaction of the vicinal methine protons H^a and H^b (Fig. 3). As it turned out later, the relative stereochemistry of compounds **18**, designed as precursors for post-Cushman transformations, was unimportant as one of the stereocenters was destroyed in the next step (vide infra).

For the deprotection–cyclization step that was central to this study, we screened a number of conditions using the model ester **18a**. Attempts to obtain the cyclized product **19a** in glacial acetic acid (similar to our earlier work[19]), as well as on basifying the TFA salts of the deprotected amines under aqueous conditions failed. To our delight, in situ basification with triethylamine in the presence of molecular sieves as a water scavenger[20] led to the desired product **19a**, which was isolated in 75% yield (Table 1). Based on its ^{1}H NMR spectrum (in which the signal corresponding to the H^b proton of the Cushman precursor was no longer present), it was shown to exist in the enamine (rather than Schiff base) form (Scheme 2). Thus, one of the stereocenters generated in the Cushman step was destroyed (thereby also removing any potential ambiguity about the diastereochemical outcome of the latter).

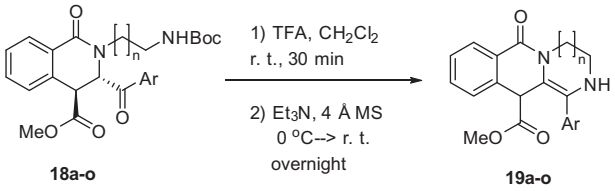
Using the newly identified conditions for the post-Cushman cyclization step, we transformed esters **18a–o** into a set of nine pyrazino[1,2-*b*]isoquinolin-6-ones (**19a–i**) and six diazepino[1,2-*b*]isoquinolin-7-ones (**19j–o**) that were obtained in moderate to excellent yields (Scheme 3).[21] The yields of the cyclization were markedly lower for the diazepino-fused compounds (Table 2). Compounds **19a–o** are based on novel scaffolds; they contain phenyl substitutents and the newly formed six- or seven-membered ring as diversity elements. Further product diversity can be potentially achieved via the use of substituted homophthalic anhydrides

Table 1
Screening of the conditions for the **18a** → **19a** cyclization

Acid	Solvent	Temp (°C)	Reaction time	Neutralization–cyclization conditions	Result
Glacial AcOH	Neat	100	4 h	—	No reaction
Glacial AcOH	Neat	200 (MW)	1 h	—	No reaction
TsOH	Toluene	110	Overnight	—	Complex mixture
TFA	CH_2Cl_2	rt	10 min	K_2CO_3	Complex mixture
TFA	Neat	rt	3 h	30% aq NaOH	Complex mixture
TFA	CH_2Cl_2	0 °C → rt	10 min (TFA) then overnight (Et_3N, 4 Å MS)	Et_3N, 4 Å MS	75% yield of **19a**

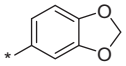
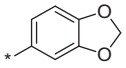


Scheme 2. Model system **18a** to identify workable cyclization conditions.



Scheme 3. Cyclization of Cushman reaction derived esters **18a–o**.

Table 2
Compounds **18a–o** and **19a–o** prepared in this work

Compound	Ar	*n*	Yield of **18** (%)	Yield of **19** (%)
18a/19a	Ph	1	47	75
18b/19b	4-FC_6H_4	1	68	91
18c/19c	3-FC_6H_4	1	60	66
18d/19d	3,4-$DiFC_6H_3$	1	56	78
18e/19e	2-$MeOC_6H_4$	1	42	78
18f/19f	3-$MeOC_6H_4$	1	69	65
18g/19g	4-$MeOC_6H_4$	1	69	44
18h/19h	3,4-$Di(MeO)_2C_6H_4$	1	56	88
18i/19i		1	39	54
18j/19j	3-$F_3CC_6H_4$	1	79	90
18k/19k	Ph	2	83	45
18l/19l	4-FC_6H_4	2	68	34
18m/19m		2	92	43
18n/19n	3,4-$Di(MeO)_2C_6H_4$	2	87	46
18o/19o	3,4-$DiFC_6H_3$	2	66	51

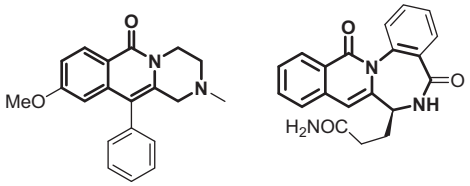


Figure 4. Examples of known biologically active compounds related to compounds **19a–o**.

in the Cushman step, as well as by manipulation of the ester and enamine functionalities.

In summary, we have reported a convenient synthesis of novel scaffolds that is based on the Cushman MCR (wherein aryl glyoxals were used as the carbonyl component for the first time), followed by post-MCR cyclization. With this route to a new chemistry space available to us, we will focus on studying further opportunities for modifying these scaffolds as well as identifying their utility as tools for modulating various biological targets (at this point, it should be noted that compounds **19a–i** are related to Merck's potassium channel blockers represented by structure **20**,[22] while compounds **19j–o** resemble the cytotoxic alkaloid, auranomide C (**21**), isolated in China from the marine-derived fungus, *Penicillium auratiogriseum*,[23] Fig. 4). The results of these efforts will be reported in due course.

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Supplementary data

Supplementary data (NMR spectra of Cushman reaction-derived esters **18a–o**, as well as the products of their cyclization (**19a–o**)) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.02.099.

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21. *Characterization data for representative compounds*: **19a**—waxy solid, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, J = 7.7 Hz, 1H), 7.82 (d, J = 7.2 Hz, 2H), 7.44 (t, J = 7.4 Hz, 2H), 7.38 (t, J = 7.6 Hz, 2H), 7.34 (t, J = 7.7 Hz, 1H), 7.26 (d, J = 7.6 Hz, 1H), 5.37 (br s, 1H), 4.54 (dd, J = 13.5, 4.5 Hz, 1H), 4.12 (s, 1H), 3.98 (dd, J = 16.9, 3.4 Hz, 1H), 3.65 (ddd, J = 16.9, 11.8, 4.5 Hz, 1H), 3.41 (s, 3H), 2.95 (ddd, J = 13.5, 11.8, 3.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.5, 165.0, 162.9, 137.3, 132.8, 131.5, 129.8, 129.2, 129.1, 128.6, 128.2, 127.0, 80.3, 53.1, 52.2, 48.5, 33.6; HRMS m/z calcd for $C_{20}H_{19}N_2O_3$ ($M+H^+$) 335.3860, found 335.3799; **19j**—grey solid, mp = 86–88 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11–8.07 (m, 2H), 7.91 (d, J = 7.8 Hz, 1H), 7.72 (d, J = 7.7 Hz, 1H), 7.51 (t, J = 8.0 Hz, 1H), 7.45 (t, J = 7.6 Hz, 1H), 7.31 (t, J = 7.5 Hz, 1H), 7.25 (d, J = 7.8 Hz, 1H), 5.65 (br s, 1H), 4.58 (dd, J = 13.3, 4.5 Hz, 1H), 4.06 (dd, J = 17.0, 3.3 Hz, 1H), 4.02 (s, 1H), 3.68 (ddd, J = 16.8, 11.8, 4.7 Hz, 1H), 3.43 (s, 3H), 3.04 (ddd, J = 13.4, 11.8, 3.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.3, 164.2, 162.9, 137.9, 133.0, 132.4, 131.3, 130.6 (q, J = 32.5 Hz), 129.2, 128.8, 128.7, 127.8, 126.5 (q, J = 3.1 Hz), 126.3 (q,

J = 4.0 Hz), 123.9 (q, *J* = 272.3 Hz), 80.4, 53.1, 52.3, 48.6, 33.7; HRMS *m*/*z* calcd for $C_{21}H_{18}F_3N_2O_3$ ($M+H^+$) 403.3844, found 403.3873; **19m**—viscous oil; ^1H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, *J* = 7.6 Hz, 1H), 7.47 (t, *J* = 7.3 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 1H), 7.28–7.23 (m, 2H), 7.18 (d, *J* = 7.3 Hz, 1H), 6.84 (d, *J* = 8.0 Hz, 1H), 5.99 (s, 2H), 4.43 (dd, *J* = 14.3, 7.8 Hz, 1H), 4.29 (s, 1H), 3.95–3.81 (m, 2H), 3.65 (s, 3H), 3.20 (ddd, *J* = 14.3, 11.5, 6.9 Hz, 1H), 2.27–2.17 (m, 1H), 2.01–1.90 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.2, 166.2, 163.3, 148.2, 147.2, 133.3, 132.4, 131.6, 128.8, 128.5, 128.3, 128.1, 123.2, 109.8, 107.8, 101.2, 90.8, 54.4, 52.9, 46.3, 39.8, 24.9; HRMS *m*/*z* calcd for $C_{22}H_{21}N_2O_5$ ($M+H^+$) 393.4231, found 393.4255.

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