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Expeditious Metal-Free Access to Functionalized Polycyclic Acetals under Mild Aqueous Conditions

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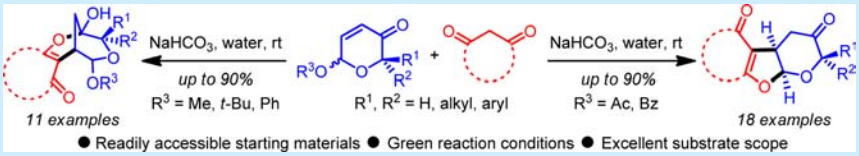
Supporting Information



ABSTRACT: A facile approach for the synthesis of furopyrans and bicyclic bisacetals under mild aqueous conditions is described. This potentially green, diversity oriented approach involves cascade Michael addition and cycloacetalization of pyranones and 1,3-dicarbonyls. An interesting switch in the product class was observed depending on the type of pyranone employed. Products of type **I** and **II** obtained herein are an integral part of several bioactive natural products and medicinally interesting compounds.

Traditional medicinal chemistry leading to drug discovery involves the study of complex biological processes by the interaction of small drug-like molecules. Toward this, diversity oriented synthesis (DOS), introduced by Schreiber, has emerged as a powerful tool to rapidly populate skeletally complex and stereochemically diverse small molecules.[1] DOS pathways have the potential to assemble privileged substructures which are an essential part of complex molecules often employed in drug discovery processes. For example, heteroannular acetals are part of a diverse range of natural products and several pharmaceuticals.[2] Among fused bicyclic acetals, tetrahydrofuro[2,3-*b*]pyrans (or furopyrans) are an important subunit embodied in many biologically significant compounds; notable examples include striatins, striatals, erinacine J, pittosporatobiraside A, daphnodorins, etc. (Figure 1).[3] The presence of intricate structural features coupled with biological activities have made these oxabicycles interesting and challenging synthetic targets. Consequently, a myriad of impressive approaches were developed to access different types of heteroannular acetals.[2,4] Although the existing methods have contributed significantly to the development of this area, these methods have several drawbacks, viz., poor substrate scope often associated with low yields, difficult-to-access starting materials, lack of atom and step economy, metal mediated reactions, etc.

Development of novel cascade processes has received great attention owing to their ability to rapidly assemble complex molecular architectures.[5] Environmentally friendly variants of such cascade reactions would further add to their significance. Against this background and in continuation of expanding our earlier studies[6] on the chemistry of heteroaryl carbinols, we initiated a program to develop a general methodology for the development of a potentially green and diversity oriented approach toward the synthesis of unprecedented heteroannular acetals of general structures **I** and **II** (Figure 1).

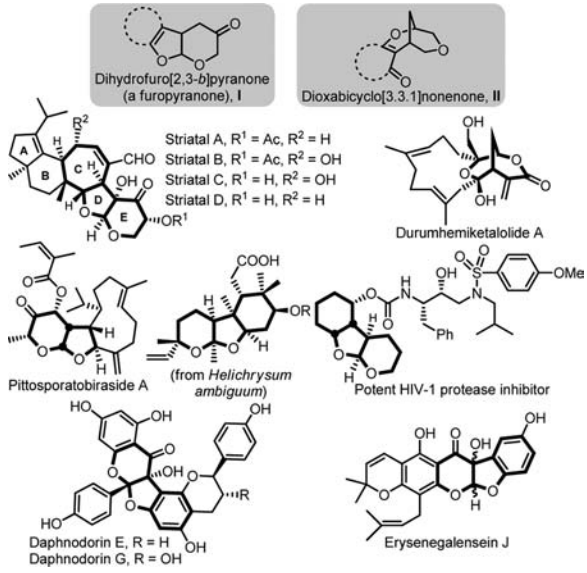


Figure 1. Some natural products and medicinally interesting compounds under the purview of this methodology.

In order to optimize the reaction conditions that could lead to the one-pot synthesis of furopyrans, in a previously unexplored approach, reaction of the acetoxy pyranone **1a**[7] and acetylacetone **2a** was chosen as the model to screen different base mediated conditions. It was envisaged that, under basic conditions, 1,3-dicarbonyls could potentially undergo Michael addition followed by concomitant cycloacetalization[8] via the cyclization of enols and *in situ* generated oxonium ions.

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Accordingly, as shown in Table 1, various base and solvent combinations were investigated. Initially when DBU was employed as a base in tetrahydrofuran solvent, gratifyingly indeed, the bicyclic acetal **3a** was isolated in 73% yield (Table 1, entry 1). The structure of **3a** (including the expected *cis* ring fusion with an unusually high *J* value of 8.8 Hz) was deduced in conjunction with the spectral data and was further confirmed unambiguously by the single crystal X-ray diffraction analysis (see Supporting Information (SI)).[9] Encouraged by this result, we set out to optimize reaction parameters for the conversion of acetate **1a** to the bicyclic acetal **3a**. Reaction in the presence of organic bases such as triethylamine (and pyridine) resulted in the formation of only the Michael addition product (Table 1, entry 2). Subsequent Brønsted base screening led to the identification of eco-friendly, cheap, and readily available sodium bicarbonate suitable for the conversion of **1a** to **3a** (Table 1, entries 3−8). We were especially delighted when substantial improvement in the yield was observed with sodium bicarbonate in water as the medium (Table 1, entry 9). Further efforts to improve the yield were not successful. For example, conducting the reaction in brine or the presence of surfactants (Table 1, entries 10−13) could not improve the yield. Solvent-free conditions were found to be encouraging but not appealing due to the moderate yield (Table 1, entry 14). As expected, no product formation was observed in the absence of a base (Table 1, entry 15).

Thus, we have identified via this comprehensive screening that 2 equiv of sodium bicarbonate under aqueous conditions at room temperature are most suitable conditions for obtaining polycyclic acetals from acetyloxy pyranones. It is worth mentioning that biomass derived starting materials and "Green" reaction conditions represent a truly sustainable method.

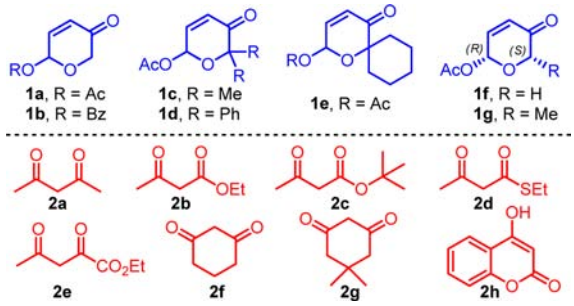
Having obtained the optimized conditions, we further examined the scope of the reaction initially with a variety of *carbonyloxy pyranones* and 1,3-dicarbonyls (Table 2). Evidently, complex di-, tri-, and tetracyclic and spirocyclic furopyranones can be accessed via this methodology in a merely single step maneuver. For example, reaction of pyranones **1a**−**1e** with *β*-

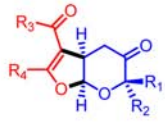
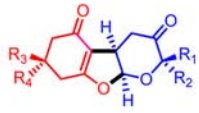
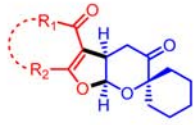
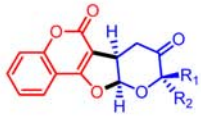
Table 1. Investigation of the Reaction Parameters[a]

entry	base (2.2 equiv)	solvent	time [h]	yield [%][b]
1	DBU	THF	1	73
2[c]	Et_3N	THF	12	–
3[d]	K_2CO_3	THF	1	75
4	Cs_2CO_3	THF	1	54
5	$NaHCO_3$	THF	3	50
6	$NaHCO_3$	MeOH	1	55
7	$NaHCO_3$	DMF	2	62
8[e]	$NaHCO_3$	THF+water	1	70
9	**$NaHCO_3$**	**water**	**1**	**88**
10	$NaHCO_3$	brine	1	73
11[f]	$NaHCO_3$	water	1	78
12[g]	$NaHCO_3$	water	1	78
13[h]	$NaHCO_3$	water	1	80
14	$NaHCO_3$	–	1	64
15	–	water	120	–

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.22 mmol), and base (0.44 mmol) in 1 mL of solvent were stirred at room temperature for an appropriate time. [b]Isolated yield after silica gel column chromatography. [c]Only Michael adduct was obtained. [d]1 equiv of 18-C-6 was used. [e]THF/water 2:3; 1 equiv of TBAI was used. [f]In presence of 20 mol % sodium dodecyl sulfate (SDS). [g]1 equiv of SDS was added. [h]In presence of 20 mol % Triton X-100.

Table 2. Scope of Various Pyranones and 1,3-Dicarbonyls[a]



entry	reactants	product	*t* (h) (% yield)
			
1	**1b** + **2a**	**3a**; R^1, R^2 = H; R^3, R^4 = Me	4 (90)
2[b]	**1a** + **2b**	**3b**; R^1, R^2 = H, R^3 = OEt, R^4 = Me	3 (90)
3	**1a** + **2c**	**3c**; R^1, R^2 = H, R^3 = O*t*-Bu, R^4 = Me	15 (72)
4	**1c** + **2d**	**3d**; R^1, R^2 = Me, R^3 = SEt, R^4 = Me	1 (72)
5	**1a** + **2e**	**3e** + **3e'**; R^1, R^2 = H, R^3 = Me, R^4 = CO_2Et + R^1, R^2 = H, R^3 = CO_2Et, R^4 = Me (3:1)	0.5 (50)
6	**1c** + **2a**	**3f**; R^1, R^2, R^3, R^4 = Me	0.5 (80)
7[c]	**1d** + **2a**	**3g**; R^1, R^2 = Ph; R^3, R^4 = Me	24 (75)
			
8	**1a** + **2f**	**3h**; R^1, R^2, R^3, R^4 = H	1 (81)
9	**1b** + **2f**	**3h**; R^1, R^2, R^3, R^4 = H	9 (52)
10	**1c** + **2f**	**3i**; R^1, R^2 = Me; R^3, R^4 = H	0.5 (71)
11	**1a** + **2g**	**3j**; R^1, R^2 = H; R^3, R^4 = Me	1 (80)
12	**1c** + **2g**	**3k**; R^1, R^2, R^3, R^4 = Me	0.5 (70)
13	**1d** + **2f**	**3l**; R^1, R^2 = Ph; R^3, R^4 = H	24 (74)
			
14	**1e** + **2a**	**3m**; R^1, R^2 = Me	1 (77)
15	**1e** + **2d**	**3n**; R^1 = SEt, R^2 = Me	24 (52)
16	**1e** + **2g**	**3o**; R^1, R^2 = -CH_2-C(CH_3)$_2$-CH_2-	1.5 (75)
			
17	**1a** + **2h**	**3p**; R^1, R^2 = H	0.5 (56)
18[b]	**1c** + **2h**	**3q**; R^1, R^2 = Me	0.5 (51)

[a]Reaction conditions: As described in Table 1. [b]In the presence of 1 equiv of SDS. [c]Yield based on starting material recovery.

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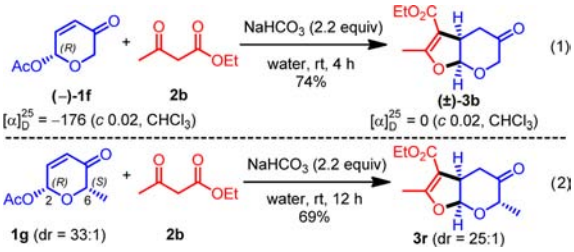
diketones and β-keto(thio)esters generated bicyclic furopyranones in good to excellent yields (Table 2, entries 1−7). Interestingly, reaction with ethyl dioxovalerate **2e** (Table 2, entry 5) furnished a 3:1 mixture of **3e** and **3e′**, originating from the two possible enol tautomers. As expected, the major product originated from the major tautomer. Pyranones **1c** and **1d** having a quaternary carbon furnished conveniently the bicyclic furopyranones in good yields (Table 2, entries 6 and 7) indicating that 1,3-spacial interactions virtually have no role in the formation of products. Functionalized tricyclic furopyranones including those containing up to two quaternary carbons can be conveniently accessed in very good yields when cyclic β-dicarbonyls are employed (Table 2, entries 8−13). The significance of this method is further established when natural product-like tetracyclic furopyrans including tetracyclic spirocycles are generated (Table 2, entries 14−18). For example, the reaction of diketone **1e** and acetate **2f** furnished tetracyclic spirofuropyranone **3o** in very good yield (Table 2, entry 16). Upon reaction, rather hydrophobic hydroxycoumarin **2h** with acetates **1a** and **1c** resulted in the formation of complex tetracyclic furopyranones **3p** and **3q**, respectively, in moderate yields (Table 2, entries 17 and 18).

Apart from the acetates of pyranones as reactants, respective benzoates were also subjected under optimized conditions, however, yielding inconsistent results. While the reaction of benzoate **1b** with diketone **2a** generated the furopyranone **3a** in 90% yield (Table 2, entry 1) [88% with acetate **1a** (Table 1, entry 9)], the reaction of benzoate **1b** with diketone **2f** furnished the tricyclic furopyranone **3h** only in 52% yield (Table 2, entry 9) [81% with acetate **1a** (Table 1, entry 8)]. Lower yields are attributed to the hydrophobicity of pyranones rendered especially by the benzoate moiety. Thus, due to their consistency as well as ease of synthesis and handling, acetates of pyranones were preferred over benzoates in this study.

To gain mechanistic insight, chiral acetates **1f** and **1g** were synthesized (Scheme 1).[10] Reaction of (*R*)-**1f** with ethyl

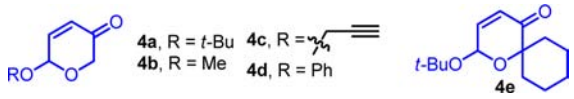
Scheme 1. Efforts To Gain Insight about the Reaction

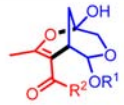
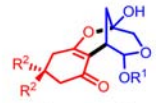
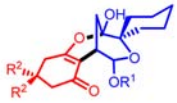


acetoacetate **2b** (Scheme 1, eq 1) generated furopyranone **3b** as a completely racemic mixture indicating that the acetalization step clearly proceeds via a preformed oxonium ion intermediate (S_N1 pathway) and the possibility of an S_N2 pathway can be ruled out.[11] On the other hand, the reaction of (2*R*,6*S*)-**1g** obtained in 33:1 dr generated furopyranone **3r** in 25:1 dr (Scheme 1, eq 2) indicating that the S_N1 pathway prevails. Further, the existence of an oxidopyrylium intermediate can be ruled out under the (mild) reaction conditions.

At this stage, we were curious about the fate of *alkoxy and aryloxy pyranones* under the optimized conditions. Accordingly, pyranones **4a**−**4e** were prepared as per literature methods.[10] Reaction of the *tert*-butoxy pyranone **4a** with the diketone **2a**, surprisingly, generated the bicyclic bisacetal **5a** in very good yield (Table 3, entry 1), whose structure was deduced from careful

Table 3. Scope of Various Alkoxy/Aryloxy Pyranones and 1,3-Dicarbonyls[a]



entry	reactants	product	t (h)	yield (%)
				
1	**2a** + **4a**	**5a**; R^1 = *t*-Bu, R^2 = Me	0.5	84
2	**2b** + **4a**	**5b**; R^1 = *t*-Bu, R^2 = OEt	4	76
3	**2b** + **4c**	**5c**; R^1 = propargyl, R^2 = OEt	2	60
				
4	**2f** + **4a**	**5d**; R^1 = *t*-Bu, R^2 = H	0.5	76
5	**2g** + **4a**	**5e**; R^1 = *t*-Bu, R^2 = Me	1	90
6	**2f** + **4b**	**5f**; R^1 = Me, R^2 = H	1	53
7	**2f** + **4c**	**5g**; R^1 = propargyl, R^2 = H	1	81
8	**2g** + **4c**	**5h**; R^1 = propargyl, R^2 = Me	0.5	65
9	**2f** + **4d**	**5i**; R^1 = Ph, R^2 = H	1	55
				
10	**2f** + **4e**	**5j**; R^1 = *t*-Bu, R^2 = H	15	68
11	**2g** + **4e**	**5k**; R^1 = *t*-Bu, R^2 = Me	48	63

[a]Reaction conditions: As described in Table 1.

analysis of the spectral data. The formation of a sensitive yet stable product possessing unusual bridgehead hemiketal and acetal functionalities points to the apparent nonformation of an oxonium ion (unlike the carbonyloxy pyranones) and eventual cyclization of the enol onto ketone leading to the formation of the hemiketal **5a**. Very pleasingly, this reaction was found to be quite general and a variety of functionalized bi-, tri-, and tetracyclic bisacetals can be obtained with the proper choice of pyran acetals and 1,3-dicarbonyls (**5b**−**5k**) (Table 3, entries 2−11). The molecular structure of a representative example (**5d**) was unambiguously confirmed by single crystal X-ray diffraction analysis (see SI for details).[9] The 2,7-dioxabicyclo[3.3.1]nonane core thus accessed via this methodology is the substructure embodied by the durumhemiketalolide family of natural products.[3]

To further illustrate the generality and synthetic utility of this methodology, furopyranone **3h** was converted to the acetate **6** via chemo- and regioselective borohydride reduction followed by acylation of resultant alcohol (Scheme 2).[10] Hydrogenolysis of the enone **6** generated the ketoacetate **7**,[12] which comprises the carbon framework of bioactive natural products such as striatals, pittosporatobiraside, etc. and is an advanced intermediate to the synthesis of several medicinally important compounds.[3] On the other hand, pyranone **3h** was converted to the phenol **8** via copper(II) chloride mediated oxidative aromatization (Scheme 2).[10,13] Phenol **8** possesses the core structure present in flavonoid natural products such as daphnodorins and erysenegalensein J.[3]

In conclusion, we have introduced a practical and scalable method for the formation of unprecedented tetrahydrofuro[2,3-

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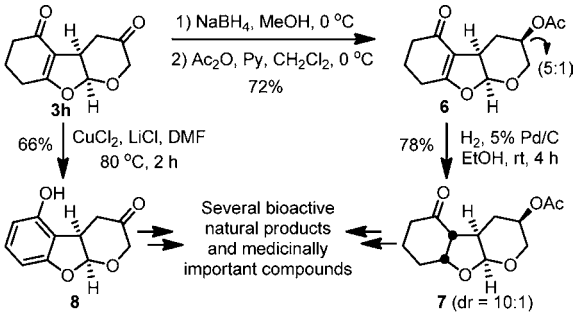
Scheme 2. Elaborations to Part Structures of Natural Products



b]pyranones and 2,7-dioxabicyclo[3.3.1]nonenones. In this diversity oriented approach, polycyclic furopyranones can be synthesized starting from readily and easily accessible 1,3-dicarbonyls and acetoxy and benzoyloxy pyranones via the Michael addition−cycloacetalization cascade under green conditions. On the other hand, under the same conditions, alkoxy and aryloxy pyranones and 1,3-dicarbonyls generate a variety of bi-, tri-, and tetracyclic bisacetals. Further investigations regarding the scope of this reaction with different nucleophiles and elaboration of these methods to the total synthesis of bioactive natural products are in progress.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectral data, and copies of ^{1}H and ^{13}C NMR spectra of all new compounds including crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(8) (a) For an isolated example undergoing Michael/cycloacetalization was reported, see: Khalilova, Y. A.; Spirikhin, L. V.; Salikhov, Sh. M.; Valeev, F. A. *Russ. J. Org. Chem.* **2014**, *50*, 117. (b) For a similar yet different reaction, see: Knol, J.; Jansen, J. F. G. A.; van Bolhuis, F.; Feringa, B. L. *Tetrahedron Lett.* **1991**, *32*, 7465.

(9) The crystal structures have been deposited at the Cambridge Crystallographic Data Centre, and the deposition numbers CCDC 1002232 (for **3a**) and CCDC 1007211 (for **5d**) have been assigned.

(10) See Supporting Information for more details.

(11) Perhaps the reaction proceeds via an initial nondiastereoselective Michael addition followed by an S_N1 pathway.

(12) The relative stereochemistries in **6** and **7** were assigned in analogy with literature reports; see: Ghosh, A. K.; Chapsal, B. D.; Baldridge, A.; Steffey, M. P.; Walters, D. E.; Koh, Y.; Amano, M.; Mitsuya, H. *J. Med. Chem.* **2011**, *54*, 622 and ref 3h.

(13) Kraus, G. A.; Johnston, B. E.; Applegate, J. M. *J. Org. Chem.* **1991**, *56*, 5688.