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Three-Component Bicyclization Providing an Expedient Access to Pyrano[2′,3′:5,6]pyrano[2,3-*b*]pyridines and Its Derivatives

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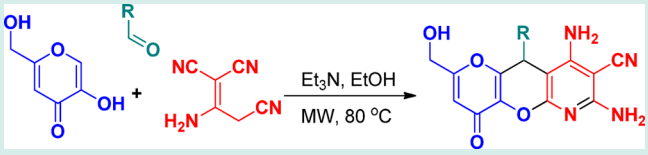
Supporting Information

ABSTRACT: A new three-component bicyclization for the efficient synthesis of a fused pyrano[2,3-*b*]pyridine library has been developed. The syntheses were achieved by reacting diverse C,O-containing nucleophiles, aldehydes, and 2-aminoprop-1-ene-1,1,3-tricarbonitrile under microwave irradiation, providing 50 examples of chemically and biomedically significant pyrano[2,3-*b*]pyridine analogues with the concomitant formation of two new rings and four σ bonds. This procedure features short reaction times, low-cost, and easily available starting materials, reliable scalability and mild reaction conditions, as well as operational simplicity.



KEYWORDS: *three-component bicyclization, bis-pyrans, pyrano[2,3-b]pyridines, microwave irradiation*

INTRODUCTION

Over the past several years, great efforts have been devoted to synthesize libraries of small heterocyclic molecules because of their high degree of structural diversity and extensive utility as therapeutic agents.[1] Bis-pyrans are key structural components, which are widespread in a myriad of natural products,[2] such as acanilol A,[3] distemonanthin,[4] and pulcherrimin[5] (Figure 1). They also occupy a pivotal place in the family of small heterocyclic molecules because of their important biological activities, including kinase and DYRK1A inhibition,[3] toxicity toward RAW and HT-29 cell lines,[5] vasoconstriction,[6] and antimycobacterial activity.[7] Therefore, we turned our attention to synthesize this type of functional bis-pyrans having biological significance. A survey of the literature revealed that there are few reports on the construction of functional bis-pyran skeleton.[8] However, to the best of our knowledge, a one-step expedient synthesis of fused pyrano[2′,3′:5,6]pyrano[2,3-*b*]-pyridines derivatives via a three-component bicyclization of kojic acid has not been reported so far.

Since the pioneering discovery of multicomponent reactions (MCRs), they have become very useful reaction protocols for the rapid and efficient construction of important molecules, as they increase the efficiency by combining several operational steps without the isolation of intermediates or changing the reaction conditions.[9] The diversity generating potential of MCRs has been recognized, and their utility in preparing libraries to screen functional molecules is well appreciated.[10] As a part of our ongoing interest in multicomponent reactions,[11] herein, we would like to report a new three-component bicyclization leading to the formation of tricyclic pyrano-[2′,3′:5,6]pyrano[2,3-*b*]pyridines in a convergent manner (Scheme 1). The present method would enable the straightforward utilization of low-cost and readily available starting materials, such as C,O-containing nucleophiles (Figure 2), aldehydes (Figure 3), and 2-aminoprop-1-ene-1,1,3-tricarbonitrile, allowing [3 + 2 + 1]-annulation and intramolecular cyclization for the efficient synthesis of functionalized bis-pyrans.

RESULTS AND DISCUSSION

The reaction of 5-hydroxy-2-(hydroxymethyl)-4*H*-pyran-4-one (kojic acid) **1**{*1*} with 4-chlorobenzaldehyde **2**{*1*}, and 2-aminoprop-1-ene-1,1,3-tricarbonitrile **3** was initially investigated by using various bases, such as K_2CO_3, Et_3N, piperidine, pyrrolidine, and *N*,*N*-dimethyl-4-aminopyridine (DMAP) under microwave (MW) irradiation. Although **4**{*1*,*1*} can be generated in the presence of all these bases, only Et_3N resulted in higher chemical yield. The reaction media, amounts of Et_3N, and reaction temperature were then examined carefully and the results were summarized in Table 1. A mixture of **1**{*1*}, **2**{*1*}, and **3** in dichloromethane (DCM) was heated under microwave irradiation at 80 °C in the presence of Et_3N (1.0 equiv) for 16 min, and the product **4**{*1*,*1*} was produced in low yield (45%) because of incomplete consumption of the reactants (Table 1, entry 1). Our attention was then shifted to investigate the effect of solvents on the product yields. DMF resulted in a good outcome (Table 1, entry 2); however, ethanol gave higher yields (Table 1, entry 3). Subsequently, the amounts of Et_3N were screened. Increasing or decreasing the amount of Et_3N gave unsatisfactory yields (Table 1, entries 4 and 5). When the reaction was carried out at 60 or 100 °C, no improvement was observed (Table 1, entries 6−7). Accordingly, the reaction of **1**{*1*}, **2**{*1*}, and **3** in EtOH was also conducted under classical heating (CH) conditions at 80 °C for

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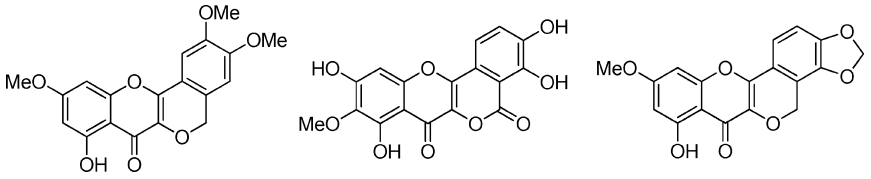
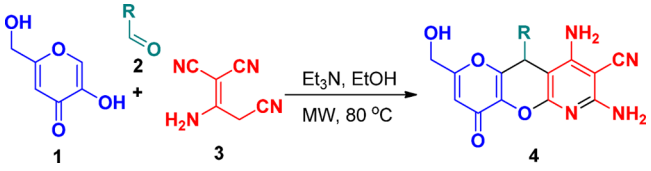


Figure 1. Several representative natural products.

Scheme 1. Domino Synthesis of Fused Pyrano[2,3-*b*]pyridines 4



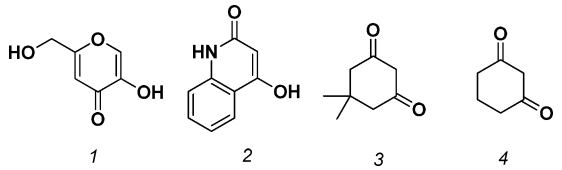
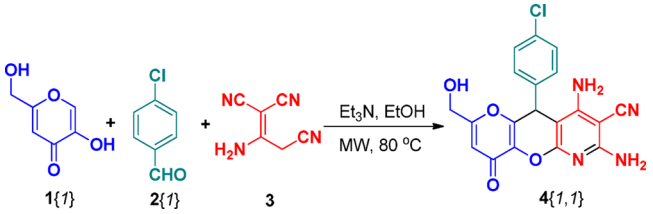


Figure 2. Diversity of C,O-containing nucleophiles **1**{*1*−*4*}.

50 min using 1.0 equiv of Et_3N as a base promoter, providing the desired product **4**{*1,1*} in 75% chemical yield (Table 1, entry 8). From the above investigations, ethanol with 1.0 equiv of Et_3N at 80 °C under microwave irradiation was established as the optimized reaction conditions for this one-step synthesis.

With the optimized reaction conditions in hand, we next explored the substrate diversity of this three-component bicyclization of 5-hydroxy-2-(hydroxymethyl)-4*H*-pyran-4-one, aldehydes, and 2-aminoprop-1-ene-1,1,3-tricarbonitrile under the optimized reaction conditions. The results were summarized in Table 2. At the beginning, the scope of aldehydes was investigated, by using 5-hydroxy-2-(hydroxymethyl)-4*H*-pyran-4-one **1**{*1*} and 2-aminoprop-1-ene-1,1,3-tricarbonitrile **3** as model substrates. Aromatic aldehydes bearing either electron-withdrawing or electron-donating substituents were well

Table 1. Optimization of Reaction Conditions under MW



entry	solvent	*t* (°C)	Et_3N (eqiv)	time (min)[a]	yield[c] (%)
1	DCM	80	1.0	16	45
2	DMF	80	1.0	16	76
3	EtOH	80	1.0	16	82
4	EtOH	80	1.5	16	80
5	EtOH	80	0.5	16	70
6	EtOH	60	1.0	16	63
7	EtOH	100	1.0	16	38
8	EtOH	80	1.0	50[b]	75

[a]Microwave (MW) irradiation. [b]Classical heating (CH) conditions. [c]Isolated yields.

tolerated under the optimized reaction conditions, providing the heterocyclic product **4** in excellent yields (Table 2, entries 1−18). The effect of steric hindrance of aromatic aldehyde did not reduce the reactivity. Also, the reactions worked well with aldehydes bearing substituents in the ortho position and the desired products were obtained. Alternatively, 4-(benzo[*d*]-oxazol-2-yl)benzaldehyde was converted into the desired fused pyrano[2,3-*b*]pyridines **4**{*1,22*} in 82% yield (Table 2, entry 19). Heteroaromatic aldehydes also showed high reactivity to afford the corresponding products in good yields (Table 2, entries 20 and 21). Similarly, aliphatic aldehydes, such as

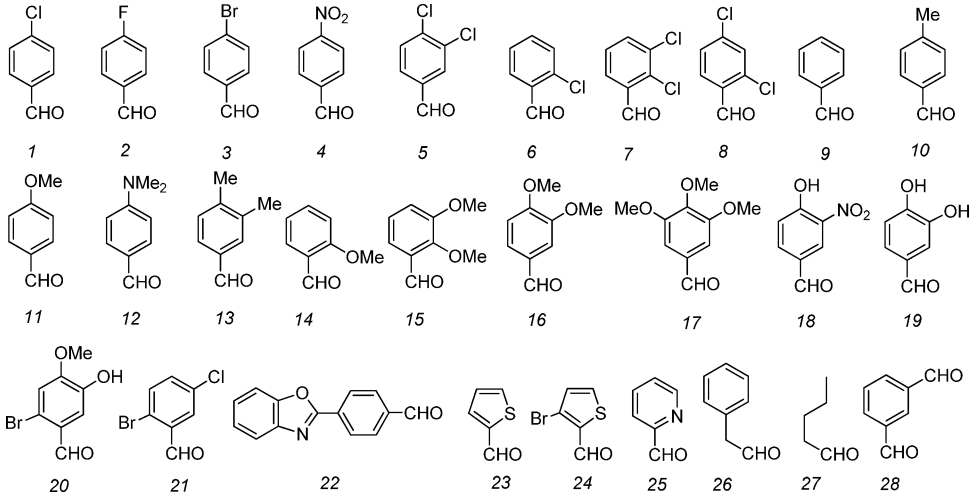


Figure 3. Diversity of aldehydes **2**{*1*−*28*}.

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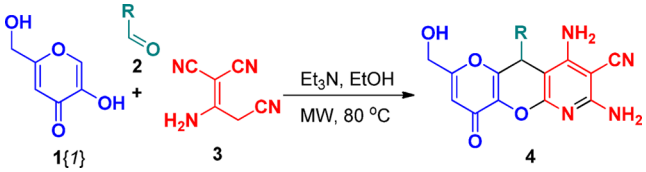
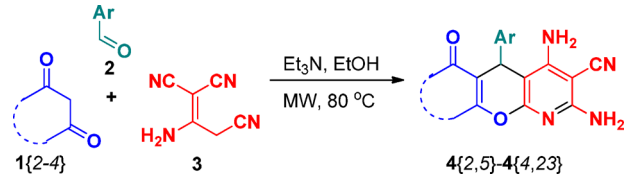
Table 2. Three-Component Bicyclization for Forming Fused Pyrano[2,3-*b*]pyridines 4



entry	product	time (min)	yield[a] (%)
1	4{*1,1*}	16	82
2	4{1,3}	17	80
3	4{*1,4*}	16	81
4	4{*1,6*}	18	79
5	4{*1,7*}	16	77
6	4{*1,9*}	19	76
7	4{*1,10*}	18	81
8	4{*1,11*}	17	82
9	4{*1,12*}	17	74
10	4{*1,13*}	18	79
11	4{*1,14*}	17	80
12	4{*1,15*}	19	81
13	4{*1,16*}	16	84
14	4{*1,17*}	17	82
15	4{*1,18*}	16	83
16	4{*1,19*}	18	79
17	4{*1,20*}	16	78
18	4{*1,21*}	19	79
19	4{*1,22*}	18	82
20	4{*1,24*}	17	83
21	4{*1,25*}	17	79
22	4{*1,26*}	18	78
23	4{*1,27*}	17	80
24	4{*1,28*}	19	81

[a]Isolated yields.

Table 3. Expanded Scope of Three-Component Bicyclization



entry	product	time (min)	yield[a] (%)
1	4{*2,5*}	16	88
2	4{*2,9*}	19	89
3	4{*2,17*}	18	92
4	4{*2,23*}	17	93
5	4{*3,1*}	16	94
6	4{*3,2*}	17	92
7	4{*3,3*}	16	93
8	4{*3,5*}	18	89
9	4{*3,8*}	17	89
10	4{*3,9*}	18	88
11	4{*3,10*}	17	90
12	4{*3,15*}	19	91
13	4{*3,16*}	20	93
14	4{*3,17*}	18	89
15	4{*3,23*}	16	88
16	4{*4,1*}	18	92
17	4{*4,2*}	17	93
18	4{*4,3*}	16	89
19	4{*4,8*}	18	88
20	4{*4,9*}	17	89
21	4{*4,10*}	17	92
22	4{*4,11*}	16	91
23	4{*4,15*}	18	93
24	4{*4,16*}	17	85
25	4{*4,17*}	19	85
26	4{*4,23*}	20	90

[a]Isolated yields.

phenylacetaldehyde and pentanal, were suitable for this domino bicyclization, affording the products **4** {*1,26*} and **4** {*1,27*} in 78% and 80% yields, respectively (Table 2, entries 22−23). Notably, treatment of isophthalaldehyde with 5-hydroxy-2-(hydroxymethyl)-4 *H*-pyran-4-one and 2-aminoprop-1-ene-1,1,3-tricarbonitrile in a 1:2:2 molar ratio gave polycyclic derivatives containing bis-pyrano[2,3- *b*]pyridine core (Table 2, entry 24). Furthermore, this special domino bicyclization provides a new route for constructing bis-pyran motif in an economical fashion, which is a valuable synthetic strategy to discover new bioactive compounds.

To further expand the scope of the current method, 4-hydroxyquinolin-2(1*H*)-one **1**{*2*}, 5,5-dimethylcyclohexane-1,3-dione **1**{*3*}, and cyclohexane-1,3-dione **1**{*4*} were examined as a replacement for the kojic acid **1**{*1*}, the reactions proceeded well and gave excellent yields. The substituent effects of the aromatic aldehydes did not hamper reaction progress. When thiophene-2-carbaldehyde was used, the desired fused pyrano[2,3-*b*]pyridine products were also produced in excellent yields (Table 3, entries 4, 15, and 26). The results exhibit the scope and generality of the new three-component bicyclization with respect to a wide range of C,O-containing nucleophiles and aldehyde substrates. It is worth mentioning that this protocol provides a direct access to functional pyrano[2,3-*b*]pyridines, which are generally prepared via multistep routes.[12]

On the basis of literature reports[12,13] and our experiments, a plausible mechanism for this three-component bicyclization was postulated in Scheme 2. First, Et_3N promoted Knoevenagel condensation between 2-aminoprop-1-ene-1,1,3-tricarbonitrile **3** and aldehydes **2** gives rise to intermediate **A**. Next, Michael addition of kojic acid **1**{*1*} to intermediate **A** occurs, followed by tautomerization and subsequent intramolecular cyclization twice, to afford final fused pyrano[2,3-*b*]pyridines **4**.

In conclusion, we have developed a facile and reliable three-component bicyclization for efficient synthesis of fused pyrano[2,3-*b*]pyridine derivatives. By using different types of commercially available C,O-containing nucleophiles with diverse aldehydes and 2-aminoprop-1-ene-1,1,3-tricarbonitrile, we could obtain novel libraries of pyrano[2,3-*b*]pyridine derivatives. This methodology is simple, practical and provides an alternative synthetic route to obtain good yields of bispyran derivatives by microwave irradiation. The separation and purification processes are very simple and convenient and the pure products were isolated by simple recrystallization. Further investigation of their biological activity is in progress.

EXPERIMENTAL PROCEDURES

General Information. Microwave irradiation was carried out with initiator 2.5 microwave synthesizers from Biotage, Uppsala, Sweden. Melting points were determined in open capillaries and were uncorrected. IR spectra were taken on a

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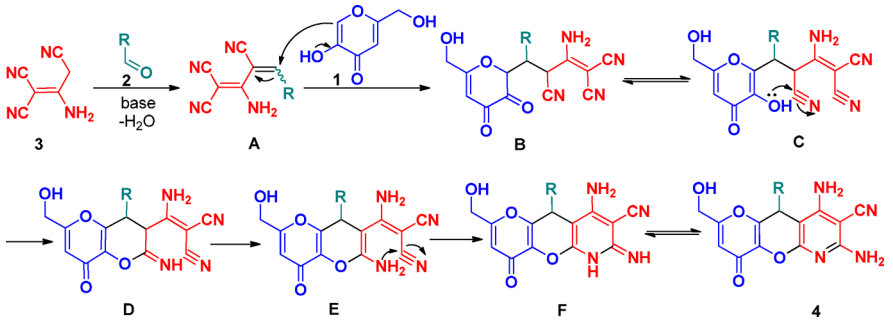
Scheme 2. Possible Mechanism for the Formation of 4



FT-IR-Tensor 27 spectrometer in KBr pellets and reported in cm^{-1}. ^1H NMR spectra were measured on a Bruker DPX 400 MHz spectrometer in DMSO-d_6 with chemical shift (δ) given in ppm relative to TMS as an internal standard. HRMS (ESI) was determined by using microTOF-Q II HRMS/MS instrument (BRUKER).

Typical Procedure for the Preparation of Bis-Pyrans 4{*1,1*}. Typically, in a 10 mL reaction vial, 5-hydroxy-2-(hydroxymethyl)-4H-pyran-4-one **1**{*1*} (0.142 g, 1.0 mmol), 4-chlorobenzaldehyde **2**{*1*} (0.140 g, 1.0 mmol), 2-aminoprop-1-ene-1,1,3-tricarbonitrile **3** (0.132 g, 1.0 mmol), and EtOH (1.5 mL), as well as Et_3N (0.101g, 1.0 mmol), were mixed and then capped. (The automatic mode of stirring helped the mixing and uniform heating of the reactants.) The mixture was heated for 16 min at 80 °C under microwave irradiation. Upon completion, monitored by TLC, the reaction mixture was then cooled to room temperature and was then neutralized by 10% HCl solution. Next, the system was diluted with cold water (50 mL). The solid was collected by Büchner filtration and was purified by recrystallization from 95% EtOH to afford the desired pure product 4{*1,1*}.

White solid. mp: >300 °C. ^1H NMR (400 MHz, DMSO-d_6) (δ, ppm): 7.40 (d, J = 8.4 Hz, 2H), 7.31 (d, J = 8.4 Hz, 2H), 6.66 (s, 2H), 6.56 (s, 2H), 6.31 (s, 1H), 5.70 (t, J = 6.0 Hz, 1H), 5.30 (s, 1H), 4.31−4.19 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 170.6, 168.3, 160.4, 158.2, 157.5, 149.8, 139.8, 137.2, 132.8, 130.1, 129.2, 116.6, 111.8, 88.4, 71.4, 59.7, 37.9. IR (KBr, ν, cm^{-1}): 3546, 3462, 3368, 3181, 2361, 2343, 2215, 1671, 1626, 1594, 1570, 1524, 1483, 1444, 1402, 1269, 1206. HRMS (ESI): m/z calcd for $C_{19}H_{12}ClN_4O_4$, 395.3547, $[M - H]^-$, found 395.0535.

■ ASSOCIATED CONTENT

Supporting Information

Further details on the experimental procedures and results. 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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