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RESEARCH ARTICLE

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Synthesis of 3,4-Dihydropyridin-2(1*H*)-ones and 3,4-Dihydro-2H-pyrans via Four-Component Reactions of Aromatic Aldehydes, Cyclic 1,3-Carbonyls, Arylamines, and Dimethyl Acetylenedicarboxylate

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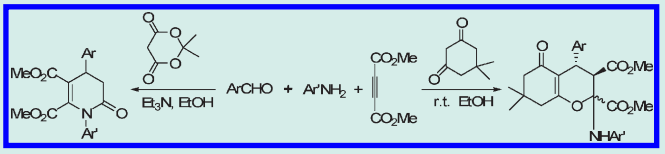
Supporting Information

ABSTRACT: A protocol has been developed for the efficient synthesis of structurally diverse 3,4-dihydropyridin-2(1*H*)-ones and 3,4-dihydro-2*H*-pyrans via four-component reactions of arylamines, acetylenedicarboxylate, aromatic aldehydes and cyclic 1,3-diketones. The selective formation of the very different pyridinone or pyran derivatives depends on the structure of cyclic 1,3-diketone. The key steps are proposed to involve Michael addition of the enamino ester formed in situ from the reaction of arylamine with dimethyl acetylenedicarboxylate to arylidine cyclic 1,3-diketones.



KEYWORDS: multicomponent reaction, 1, 3-dipolar addition, pyridinone, pyran, β-enamino ester

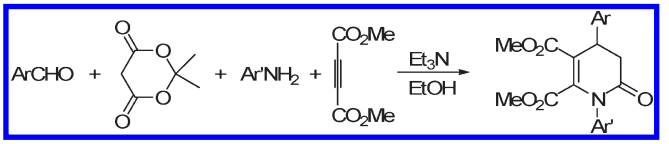
INTRODUCTION

Multicomponent reactions have received considerable attention because of their wide range of applications in organic and medical chemistry. Such reactions are able to create combinatorial libraries of complex and diverse structures in efficient fashion by virtue of their convergent nature.[1,2] Several new designed multicomponent reactions have been reported recently,[3,4] including processes that take advantage of Huisgen 1,4-dipoles formed from the addition of nitrogen heterocycles or amines to electron-deficient alkynes.[5−10] Thus, domino reactions involving primary amines, acetylenedicarboxylates, and a third component have been provided elegant procedures for the synthesis of various N- and N, O-heterocycles.[11−13] We have reported related four-component reactions of aromatic aldehydes, arylamines, acetylenedicarboxylate and acetonitrile derivatives, providing quick access to polysubstituted dihydropyridines.[14] To obtain more information about this novel multicomponent reaction and to examine its substrate scope and limitations, we replaced nitrile-activated components with cyclic 1,3-dicarbonyl compounds. We report here efficient four-component assemblies with these building blocks, producing structurally diverse 3,4-dihydropyridin-2(1*H*)-one and 3,4-dihydro-2*H*-pyran derivatives.

RESULTS AND DISCUSSION

At first we investigated the reactivity of Meldrum acid in the four-component reaction. Meldrum's acid proved to be an active component in reactions performed in ethanol solution in the presence of triethylamine as base catalyst at elevated temperature (50−60 °C) for six hours. 3,4-Dihydropyridin-2(1*H*)-ones **1a**−**1h** were produced in moderate yields (41−60%) as shown in Table 1. To increase the yields of 3,4-dihydropyridin-2(1*H*)-ones, the reaction conditions were also examined. But these trying did not provided much better results. The lower yields of the products might be due to a competitive ring-opening and subsequent decarboxylation of the Meldrum's acid moiety in hot basic solution. The four-component reaction proceeded smoothly with normal and electron-deficient aromatic amines and aldehydes. The structures of the two representative compounds (**1c** and **1h**) were determined by X-ray diffraction; the structure of **1c** is shown in Figure 1. The reaction mechanism (Scheme 1) is believed to involve Michael addition of the *1,3*-dipole

Table 1. Synthesis of Polysubstituted 3,4-Dihydropyridin-2(1*H*)-ones



entry	compd	Ar	Ar′	yield (%)[a]
1	**1a**	C_6H_5	*p*-$CH_3C_6H_4$	41
2	**1b**	*p*-$(CH_3)_2CHC_6H_4$	*p*-$CH_3C_6H_4$	46
3	**1c**	*p*-ClC_6H_4	*p*-$CH_3C_6H_4$	58
4	**1d**	*m*-ClC_6H_4	*p*-$CH_3C_6H_4$	53
5	**1e**	*m*-$NO_2C_6H_4$	*p*-$CH_3C_6H_4$	60
6	**1f**	C_6H_5	C_6H_5	45
7	**1g**	C_6H_5	*p*-ClC_6H_4	47
8	**1h**	*p*-ClC_6H_4	*p*-ClC_6H_4	52

[a] Isolated yields. All compounds were characterized by ^1H, ^{13}C NMR. Reaction conditions: Et_3N(0.5 equiv.), EtOH, 50−60 °C, 6 h.

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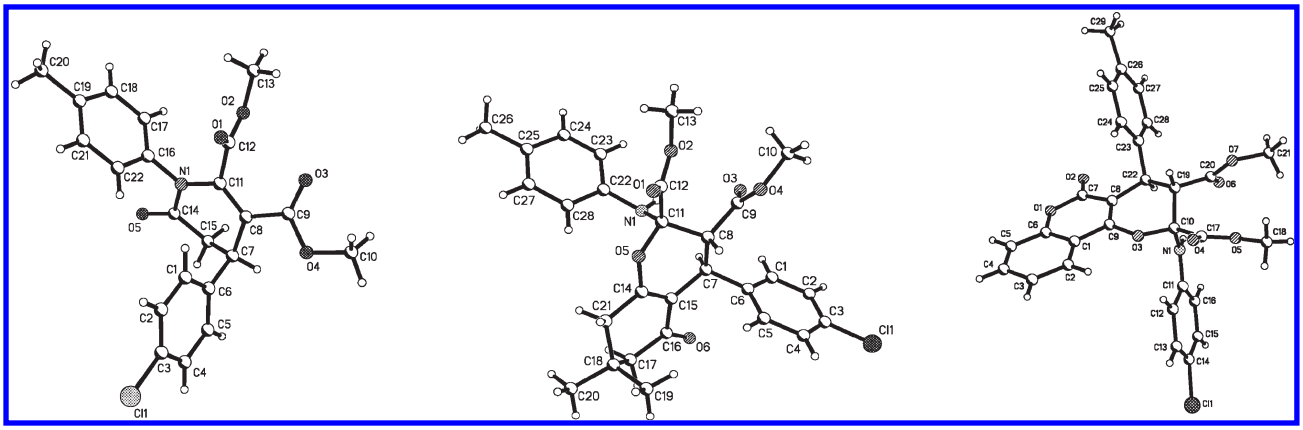
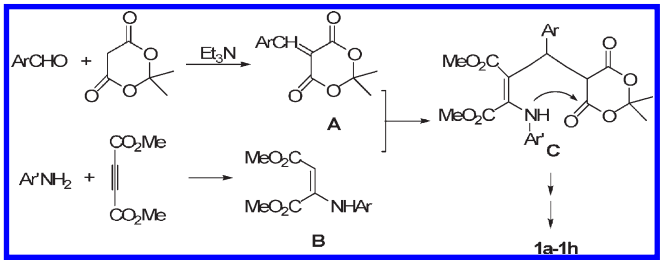


Figure 1. Molecular structure of 3,4-dihydropyridin-2(1H)-one **1c** and 3,4-dihydro-2H-pyrans **2f, 4b**.

Scheme 1. Proposed Mechanism of the Formation of 3,4-Dihydropyridin-2(1*H*)-ones



intermediate (**B**) to the arylidene Meldrum's acid condensate (**A**), followed by intramolecular nucleophilic substitution in intermediate (**C**) to form the cyclic amide with elimination of acetone and carbon dioxide. Dihydropyridinone ring system constitutes a group of natural biologically active compounds such as alkaloids which have attracted much attention owing to their wide range of biological activities. The most synthetic approaches have been concentrated on the 1,4-dihydropyridinone and its derivatives. But the synthesis of 3,4-dihydropyridin-2-one has not been explored widely and there were only limited literature precedents for their synthesis.[15,16] Here we are successfully provided an efficient route to polysubstituted 3,4-dihydropyridin-2-ones starting from readily available starting materials.

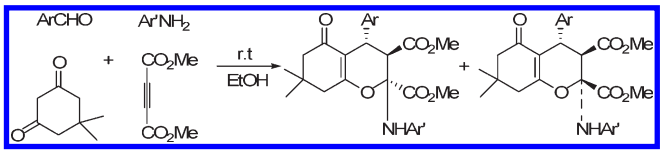
The replacement of Meldrum's acid with dimedone produced complex mixtures of products when triethylamine was used to catalyze the four-component reaction. An exploration of several parameters (including base catalyst, solvent, temperature, the sequence of addition of substrates) provided dramatic improvements. Optimal results were obtained by carrying out the four component reaction at room temperature for about one day without using any catalyst. The resulting precipitates were collected by filtration and were found to be novel polysubstituted 3,4-dihydro-2*H*-pyrans such as **2a** (Table 2). 3,4-Dihydro-2*H*-pyran moiety is a fundamental structural unit of biologically active compounds. These types of compounds have previously been accessed only by more cumbersome multistep procedures.[17−20] We are pleased to find a convenient method for the synthsis of polysusbtituted 3,4-dihydro-2*H*-pyrans via a four-component reaction. A variety of electron-poor and electron-rich aromatic aldehydes and amines were found to react very smoothly to provide the analogous dihydro-2*H*-pyrans in satisfactory yields (64−85%) as shown in Table 2.

The structures of 3,4-dihydro-2*H*-pyrans **2a**−**2m** were fully suppported by elemental analysis, ^{1}H and ^{13}C NMR, MS, and IR spectra, and were further confirmed by single-crystal X-ray diffraction studies performed on compounds **2f** (Figure 1) and **2j**. The most surprising feature of the structure of **2a**−**2m** is the fact that one carbonyl group of dimedone took part in cyclization, rather than the amino group, giving the oxygen-containing six-membered ring. Two diastereomers in each product were clearly identified in ^{1}H NMR spectra in ratios of 5:1 to 7:1, reflecting the cis/trans relationship of the two ester groups. For example, **2a** showed a doublet at 4.20 ppm for the proton at C-4 of the major (trans) isomer and a corresponding doublet at 4.33 ppm for the minor (cis) isomer; other resonances showed similar differences. The X-ray single-crystal molecular structure of **2f** and **2j** showed the aryl group at C-4, ester group at C-3 and ester group at C-2 to be in the all trans-configuration, corresponding to the major isomer of the product.

A similar reactivity pattern was observed with 1,3-cyclohexanedione and 4-hydroxycoumarin as dicarbonyl components, giving the corresponding polysubstituted 3,4-dihydro-2*H*-pyrans (**3a**−**3e**) in 66−78% yields (Table 3) and tricyclic compounds (**4a**−**4e**) in 62−75% yields (Table 3). Benzylamine was also incorporated in place of anilines in reactions with dimedone, giving 3,4-dihydro-2H-pyrans **5a**−**5j** in 63−81% yields. Taken together, these reactions provided 20 new 3,4-dihydro-2H-pyran derivatives, of which three were characterized by X-ray crystallography (**3b**, **4b** (Figure 1) and **5b**. ^{1}H NMR spectra indicated a strong preference for only one isomer, presumably that observed by crystallography having trans relationships between the two ester groups and between the aryl group at C-4 and ester at C-3.

Scheme 2 shows a plausible reaction mechanism for these multicomponent transformations, starting with the same type of Knoevenagel and Michael condensation intermediates (**A** and **B**) employed in the Meldrums acid reactions above.[17] Michael addition of 1,3-dipolar intermediate **B** to **A** should give **C**, which is isomerized to **D** by ketone-enol tautomerization. Intramolecular addition of the enolate to the electron-deficient alkene unit (or its imine/iminium tautomer, not shown) provides intermediate **E**, which in turn is converted to the final 3,4-dihydro-2H-pyran **2** by protononation. The stereochemistry of the 3,4-dihydro-2*H*-pyran is controlled by the cis/trans configuration of the in situ formed intermediate (**B**) and the three sequential reaction steps in the reaction mechanism. The addition of arylamines to but-2-enedioates has been reported to give both

Table 2. Synthesis of Polysubstituted 3,4-Dihydro-2*H*-pyrans



entry	compd	Ar	Ar′	yield (%, trans/cis)[a]
1	**2a**	C_6H_5	*p*-$CH_3C_6H_4$	71 (6:1)
2	**2b**	*p*-$CH_3C_6H_4$	*p*-$CH_3C_6H_4$	67 (6:1)
3	**2c**	*p*-$(CH_3)_2CHC_6H_4$	*p*-$CH_3C_6H_4$	72 (5:1)
4	**2d**	*p*-$CH_3OC_6H_4$	*p*-$CH_3C_6H_4$	64 (6:1)
5	**2e**	*p*-FC_6H_4	*p*-$CH_3C_6H_4$	69 (7:1)
6	**2f**	*p*-ClC_6H_4	*p*-$CH_3C_6H_4$	78 (7:1)
7	**2g**	*p*-BrC_6H_4	*p*-$CH_3C_6H_4$	75 (7:1)
8	**2h**	*m*-$NO_2C_6H_4$	*p*-$CH_3C_6H_4$	85 (7:1)
9	**2i**	*p*-$CH_3C_6H_4$	C_6H_5	62 (7:1)
10	**2j**	*p*-$CH_3C_6H_4$	*m*-ClC_6H_4	74 (6:1)
11	**2k**	*p*-$CH_3C_6H_4$	*p*-ClC_6H_4	75 (6:1)
12	**2l**	*p*-$CH_3C_6H_4$	*p*-$CH_3OC_6H_4$	76 (6:1)
13	**2m**	*p*-$(CH_3)_2NC_6H_4$	*p*-$CH_3OC_6H_4$	71 (6:1)

[a] Isolated yields. All compounds were characterized by ^1H, ^{13}C NMR. The ratios of trans/cis were estimated by ^1H NMR. Reaction conditions: EtOH, r.t., 24 h.

cis- and trans-isomers, depending on the nature of the solvent, substituent, and concentration of the reactants.[21] Recently Jiang reported 2-arylamino fumarates (trans-isomers) to be favored in protic solvents such as methanol and ethanol and the corresponding maleates (cis-isomers) to be favored in nonprotic media such as DMF.[22] In our case, the two Michael addition steps and the protonation step in Scheme 2 are all reversible and in thermodynamic equilibrium, giving rise to the more stable 2,3-trans/3,4-trans isomer as the major product. A direct hetero-Diels–Alder addition of the 1,3-dipolar intermediate (**B**) to arylidene dimedone (**A**),[23,24] could be ruled out as an alternative mechanism, since the stereochemical outcome should be different.

CONCLUSION

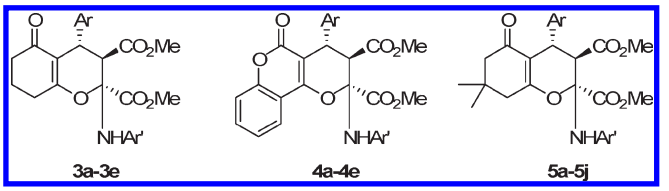
In summary, we have developed an interesting four-component reaction of aromatic aldehydes, cyclic 1,3-diketones, aryl amines, and dimethyl acetylenedicarboxylate providing two different classes of products depending on the nature of the dicarbonyl component. Mechanisms for the formation of the resulting 3,4-dihydropyridin-2(1*H*)-ones and 3,4-dihydro-2*H*-pyrans derivatives are proposed in which stereochemistry is controlled by thermodynamic factors. The potential uses of the reaction in synthetic and medicinal chemistry may be significant, since the products share structural and functional group properties with a variety of biologically active molecules. Further expansion of the reaction scope and synthetic applications of this methodology are in progress in our laboratory.

EXPERIMENTAL SECTION

1. Typical Procedure for the Four-Component Reaction of Arylamines, Dimethyl Acetylenedicarboxylate, Aromatic Aldehydes and Meldrum Acid. A mixture of aromatic aldehyde (2.0 mmol), meldrum acid (2.0 mmol, 0.288 g), and triethylamine (1.0 mmol, 0.101 g) in 5.0 mL ethanol was stirred at room for ten minutes. Then a solution of arylamine (2.0 mmol) and dimethyl acetylenedicarboxylate (2.0 mmol, 0.284 g) in 5.0 mL ethanol was added to it. The whole solution was stirred the elevated temperature (50–60 °C) for six hours. In most cases the resulting precipitates were collected by filtration and washed with cold alcohol to give the pure product for analysis. In fewer cases the products were further purified with SiO_2 thin-layer chromatograph with ethyl acetate and light petroleum (V/V = 1/3) as elute to give the product **1a**: yellow solid, 41%, mp 147–149 °C; ^1H NMR (600 MHz, $CDCl_3$) δ 7.38–7.34 (m, 4H, ArH), 7.27 (t, J = 6.6 Hz, 1H, ArH), 7.19 (d, J = 7.8 Hz, 2H, ArH), 7.05 (d, J = 6.6 Hz, 2H, ArH), 4.31 (d, J = 7.2 Hz, 1H, CH), 3.68 (s, 3H, OCH_3), 3.50 (s, 3H, OCH_3), 3.21 (dd, J_1 = 7.8 Hz, J_2 = 16.2 Hz, 1H, CH_2), 2.96 (d, J = 16.2 Hz, 1H, CH_2), 2.35 (s, 3H, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.5, 165.6, 163.3, 144.7, 139.9, 139.2, 133.3, 129.8, 129.1, 128.8, 127.5, 126.7, 109.4, 52.6, 52.3, 38.6, 36.7, 21.3; IR(KBr) υ 3021, 2953, 1739, 1707, 1633, 1506, 1433, 1347, 1300, 1257, 1204, 1146, 1112, 1069, 987, 849, 803, 754 cm^{-1}; MS (m/z) 378.26 ($[M-1]^+$) 100%. Anal. Calcd for $C_{22}H_{21}NO_5$: C 69.64, H 5.58, N 3.69; Found C 69.78, H 5.81, N 3.54.

2. Typical Procedure for the Four-Component Reaction of Arylamines, Dimethyl Acetylenedicarboxylate, Aromatic Aldehydes, and Dimedone. A mixture of arylamine (2.0 mmol) and dimethyl acetylenedicarboxylate (2.0 mmol, 0.284 g) in 5.0 mL ethanol was stirred at room for ten minutes. Then aromatic aldehyde (2.0 mmol), dimedone (2.0 mmol, 0.284 g) was added. The whole

Table 3. Synthesis of 3,4-Dihydro-2*H*-pyran Derivatives



entry	compd	Ar	Ar′	yield[a] (%)
1	**3a**	*p*-ClC_6H_4	C_6H_5	66
2	**3b**	*p*-ClC_6H_4	*p*-$CH_3C_6H_4$	71
3	**3c**	*m*-$NO_2C_6H_4$	*p*-$CH_3C_6H_4$	78
4	**3d**	*p*-ClC_6H_4	*p*-ClC_6H_4	75
5	**3e**	*p*-$CH_3C_6H_4$	*p*-$CH_3OC_6H_4$	69
6	**4a**	*p*-ClC_6H_4	*p*-$CH_3OC_6H_4$	66
7	**4b**	*m*-ClC_6H_4	*p*-$CH_3C_6H_4$	62
8	**4c**	*p*-$CH_3C_6H_4$	*p*-ClC_6H_4	70
9	**4d**	*m*-$NO_2C_6H_4$	*p*-$CH_3C_6H_4$	72
10	**4e**	*m*-$NO_2C_6H_4$	*p*-ClC_6H_4	75
11	**5a**	C_6H_5	$CH_2C_6H_5$	65
12	**5b**	*p*-$CH_3C_6H_4$	$CH_2C_6H_5$	68
13	**5c**	*p*-$(CH_3)_2CHC_6H_4$	$CH_2C_6H_5$	68
14	**5d**	*m*-$(CH_3)_3CC_6H_4$	$CH_2C_6H_5$	73
15	**5e**	*p*-$CH_3OC_6H_4$	$CH_2C_6H_5$	68
16	**5f**	*p*-FC_6H_4	$CH_2C_6H_5$	70
17	**5g**	*m*-ClC_6H_4	$CH_2C_6H_5$	63
18	**5h**	*p*-ClC_6H_4	$CH_2C_6H_5$	73
19	**5i**	*p*-BrC_6H_4	$CH_2C_6H_5$	70
20	**5j**	*m*-$NO_2C_6H_4$	$CH_2C_6H_5$	81

[a] Isolated yields. All compounds were characterized by ^1H, ^{13}C NMR. Reaction conditions: EtOH, r.t. 24 h.

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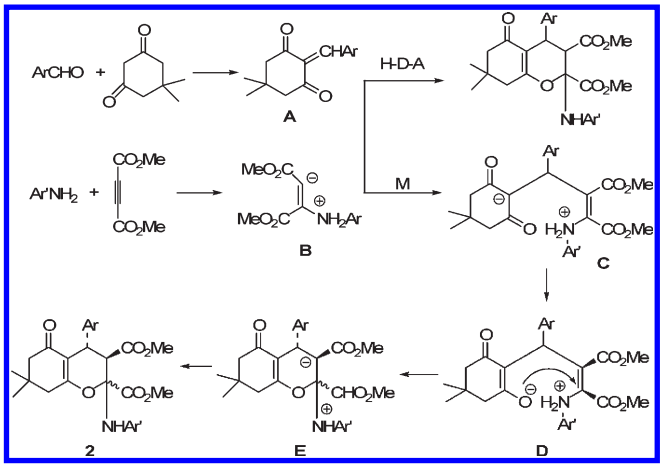
Scheme 2. Formation Mechanism of Polysubstituted 3,4-Dihydro-2*H*-pyrans



solution was stirred at room temperature for additional about 24 h. The resulting precipitates were collected by filtration and recrystallized in a mixture of ethanol and dimethyl formamide (V/V = 10/1) to give the pure product for analysis. 2a: white solid, 71%, mp 171−172 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.26−7.24 (m, 3H, ArH), 7.13 (d, J = 7.8 Hz, 2H, ArH), 6.98 (d, J = 8.4 Hz, 2H, ArH), 6.74 (d, J = 8.4 Hz, 2H, ArH), 5.44 (brs, 1H, NH), 4.20 (d, J = 10.2 Hz, 1H, CH), 3.56 (s, 3H, OCH_3), 3.51 (s, 3H, OCH_3), 3.18 (d, J = 10.2 Hz, 1H, CH), 2.60 (d, J = 17.4 Hz, 1H, CH_2), 2.34 (d, J = 17.4 Hz, 1H, CH_2), 2.24 (s, 3H, CH_3), 2.17 (s, 2H, CH_2), 1.15 (s, 3H, CH_3), 1.01 (s, 3H, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 195.9, 171.5, 168.7, 166.5, 141.2, 140.8, 129.7, 128.6, 128.2, 127.2, 126.9, 126.8, 125.9, 115.6, 113.3, 87.8, 54.1, 53.1, 52.6, 50.7, 42.0, 38.8, 31.7, 31.4, 29.2, 27.6, 20.5; IR(KBr) υ 3391, 3022, 2960, 2876, 1759, 1729, 1643, 1592, 1519, 1434, 1370, 1348, 1317, 1265, 1232, 1168, 1047, 1006, 940, 820, 756 cm^{-1}; MS (m/z) 478.55 ($[M + 1]^+$) 100%. Anal. Calcd for $C_{28}H_{31}NO_6$: C 70.42, H 6.54, N 2.93; Found C 70.35, H 6.82, N 2.71. The same reaction procedure was carried out by using other cyclic 1,3-dicarbonyl compounds and other amines in the reactions to give 3,4-dihydro-2H-pyran derivatives **2b**−**2m**, **3a**−**3e**, **4a**−**4e**, and **5a**−**5j**.

■ ASSOCIATED CONTENT

Supporting Information. The experimental details and the spectroscopic data, including crystallographic data (CIF) of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

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Funding Sources

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