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Facile synthesis of polysubstituted furans and dihydrofurans via cyclization of bromonitromethane with oxodienes

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ABSTRACT

A series of polysubstituted furans and dihydrofurans have been prepared from readily available oxodienes and bromonitromethane in modest to excellent yields. This facile synthetic method is developed on the basis of proprietary properties of nitro group such as strong electron-withdrawing ability and cleavability. The conversion of nitro-substituted dihydrofurans to furans is presumably realized by elimination of HNO_2 under the aid of DABCO.

Introduction

Polysubstituted furans or dihydrofurans are important heterocycles commonly found in a large variety of naturally occurring substances.[1] Furans play a vital role in organic chemistry due to their wide applications as building blocks[2] as well as versatile biological activities.[3] For these reasons, the development of new and efficient methods for the synthesis of polysubstituted furans remains an area of current interest and a whole series of new synthetic methods have appeared in literatures.[4] Classical synthetic methods for synthesizing furans include Paal-Knorr synthesis[5] and Feist-Benary synthesis[6] from dicarbonyl compounds. During the past decades, an enormous increase of efficient approaches to polysubstituted furans included the transition-metal-catalyzed reactions of alkynyl,[7] allenyl,[8] or other derivatives.[9] In addition, a series of [3+2][10] and [4+1][11] annulation reactions or multicomponent reactions[12] have been developed for the synthesis of substituted furans. However, the exploration of new methods for the synthesis of polysubstituted furans is still highly desirable.

Nitroalkanes,[13] nitroalkenes[14] and nitroallylic acetates[15] have proven to be versatile synthons in organic synthesis due to the strong electron-withdrawing ability and cleavability of nitro group. Considering the special reactivity of the nitro functional group[16] and its ease of conversion into other important structural motifs,[17] we were interested in bromonitroalkanes, the useful analogs of nitroalkanes. As part of our continuous efforts to develop new synthetic methods for cyclic compounds,[18] Herein, we report an easy synthetic strategy to achieve furans and nitro-substituted dihydrofurans via cyclization of bromonitromethane with oxodienes.

Results and discussion

We started our investigation with the reaction of bromonitromethane **1a** and oxodiene **2a** (Table 1). In the presence of DABCO (0.3 mmol) and K_2CO_3 (0.3 mmol), a reaction mixture of **1a** (0.45 mmol) and **2a** (0.3 mmol) in toluene (2.0 mL) was stirred at room temperature for 12 h. To our delight, trisubstituted furan **3a**, nitro-substituted dihydrofuran **4a** and cyclopropane **5a** were achieved in 20%, 27% and 3% yields, respectively (entry 1). Without DABCO, however, only dihydrofuran **4a** and cyclopropane derivative **5a** were obtained (entry 2). Obviously, DABCO plays an important role in the formation of **3a**. Actually, DABCO itself can lead to the formation of the furans, dihydrofurans and cyclopropanes. Interestingly, the ratio of products depends on the amount of DABCO (entries 3–4). Other organic bases such as DMAP, DBU and NEt_3 can also facilitate this reaction although with relative lower yields (entries 5–7). Common solvents like THF, CH_3CN, and $CHCl_3$ could readily afford the products (entries 8–10). With THF chosen as the solvent, we next conducted the reaction with K_2CO_3 (0.3 mmol) alone for 12 h at room temperature, then

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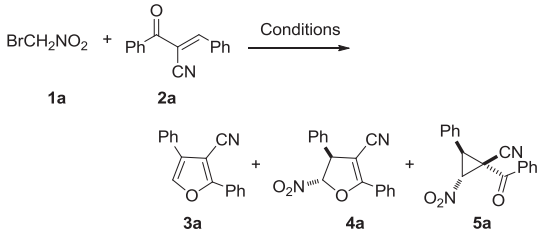
Table 1
Optimization of conditions for chemoselective formation of **3a**.[a]



Entry	DABCO (mmol)	K_2CO_3 (mmol)	Solvent	**3** (%)[b]	**4** (%)[b]	**5** (%)[b]
1	0.3	0.3	Toluene	20	27	3
2	none	0.3	Toluene	trace	47	27
3	0.6	none	Toluene	18	38	6
4	1.5	none	Toluene	45	trace	trace
5[c]	0.6	none	Toluene	8	31	trace
6[d]	0.6	none	Toluene	11	24	trace
7[e]	0.6	none	Toluene	7	46	5
8	0.3	0.3	THF	14	45	3
9	0.3	0.3	CH_3CN	18	27	trace
10	0.3	0.3	$CHCl_3$	1	42	trace
11[f]	0.6	0.3	THF	71	trace	trace

[a] Typical procedure: to a mixture of **2a** (0.3 mmol), DABCO and K_2CO_3 (0.3 mmol) in specific solvent (2.0 mL) was added bromonitromethane **1a** (0.45 mmol), and the resulting mixture was stirred at room temperature for 12 h.
[b] Isolated yield based on **2a**.
[c] DMAP was used instead of DABCO.
[d] DBU was used instead of DABCO.
[e] NEt_3 was used instead of DABCO.
[f] To a mixture of **2a** (0.3 mmol), K_2CO_3 (0.3 mmol) in THF (2.0 mL) was added bromonitromethane **1a** (0.45 mmol), and the resulting mixture was stirred at room temperature for 12 h, then DABCO (0.6 mmol) was added, the resulting mixture was stirred at room temperature for another 24 h.

0.6 mmol DABCO was added, the mixture was reacted for additional 24 h, the yield of **3a** could be improved to 71% (entry 11). Thus, the preferable conditions were established.

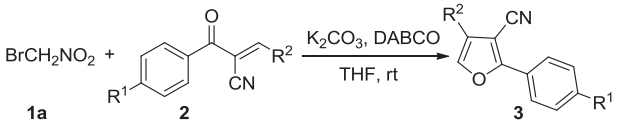
Having identified the optimal conditions, we next set out to examine the scope and limitations of this reaction. The results are summarized in Table 2. A variety of oxodienes bearing electron-donating substituent (CH_3) or electron-withdrawing substituents (F, Cl, Br) at the phenyl ring worked well, providing the trisubstituted furans **3** in good to excellent yields, while compound **2f** showed lower reactivity presumably due to the strong electron-withdrawing ability of CF_3 group (entries 1–6). Heteroaryl substituted alkenes were effective candidates to give the corresponding products in moderate yields (entries 7–8). Good results can also be obtained when R^1 bearing electron-donating substituents or electron-withdrawing substituent (entries 9–17).

It is worthy to note that when **1b** was used instead of **1a**, tetrasubstituted furans **6** were achieved in good yields under the standard conditions (Scheme 1).

One-pot synthesis of **3a** was successfully furnished by mixing readily available 3-oxo-3-phenylpropanenitrile (0.3 mmol), benzaldehyde (0.3 mmol) and DABCO (1.2 mmol) in THF (2.0 mL), and the resulting mixture was stirred at room temperature for 12 h, then bromonitromethane **1a** (0.45 mmol) was added, the resulting mixture was stirred at room temperature for another 6 h. The furan product was isolated in 33% total yield (Scheme 2).

Dihydrofurans or cyclopropanes serve as useful intermediates[19] for organic transformations and are widely found in natural products and pharmaceuticals.[20] Next, we try to optimize the reaction conditions so that we can easily achieve nitro-substituted dihydrofurans and cyclopropanes from the same starting materials. As can be seen in Table 3, the amount of inorganic base has a significant

Table 2
Synthesis of furans **3** from bromonitromethane **1a** and oxodienes **2**.[a]



Entry	R^1 in **2**	R^2 in **2**	**3**, Yield (%)[b]
1	H	Ph (**2a**)	**3a**, 71
2	H	4-$CH_3C_6H_4$ (**2b**)	**3b**, 84
3	H	4-FC_6H_4 (**2c**)	**3c**, 77
4	H	4-ClC_6H_4 (**2d**)	**3d**, 76
5	H	4-BrC_6H_4 (**2e**)	**3e**, 85
6	H	4-$CF_3C_6H_4$ (**2f**)	**3f**, 54
7[c]	H	2-furyl (**2g**)	**3g**, 64
8[c]	H	2-thienyl (**2h**)	**3h**, 84
9	CH_3O	4-$CH_3C_6H_4$ (**2i**)	**3i**, 35
10	CH_3O	4-FC_6H_4 (**2j**)	**3j**, 41
11	CH_3O	4-ClC_6H_4 (**2k**)	**3k**, 42
12	CH_3O	3-ClC_6H_4 (**2l**)	**3l**, 57
13[c]	CH_3O	2-thienyl (**2m**)	**3m**, 62
14	CH_3	4-BrC_6H_4 (**2n**)	**3n**, 79
15	CH_3	2-ClC_6H_4 (**2o**)	**3o**, 41
16	F	4-BrC_6H_4 (**2p**)	**3p**, 74
17[c]	F	2-thienyl (**2q**)	**3q**, 81

[a] To a mixture of **2** (0.3 mmol) and K_2CO_3 (0.3 mmol) in THF (2.0 mL) was added bromonitromethane **1a** (0.45 mmol), and the resulting mixture was stirred at room temperature for 12 h, then DABCO (0.6 mmol) was added, the resulting mixture was stirred at room temperature for another 24 h.
[b] Isolated yield based on **2**.
[c] After DABCO (0.6 mmol) was added, the resulting mixture was stirred at room temperature for another 6 h.