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One-Pot Synthesis of Substituted Di-Hydrofurans from Lewis Base-Catalyzed Three-Component Condensation

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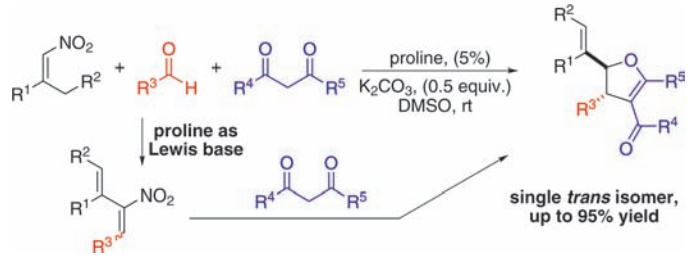
ABSTRACT



A one-pot synthesis of substituted dihydrofurans was developed through a Lewis base-catalyzed three-component cascade condensation between nitroalkenes, aldehydes, and 1,3-dicarbonyl compounds. The desired cyclization products were prepared with a large substrate scope (22 examples) and excellent diastereoselectivity (only *trans* isomers) in good to excellent yields (up to 95%).

During the last couple of years, our group has been working on the development of cascade reactions through amine-catalyzed nitroalkene activation.[1] These efforts have led to several new multicomponent condensations and the formation of various heterocycles with good to excellent yields and stereoselectivity.[2] The general process involved in this new reaction mode started from the amine addition to the nitroalkene, giving the corresponding formal allylic nitro carbanion (Scheme 1A). Through the designated β-elimination, the undesired nitroalkene polymerization was avoided and sequential addition to proper electrophiles gave the highly functionalized products with high efficiency.

Recently, another interesting condensation strategy was revealed as an extension to the amine-catalyzed nitroalkene activation (Scheme 1B). Upon the treatment of the amine Lewis base catalyst, nitroalkene could conduct nitro-aldol condensation with aldehyde, giving the nitro-diene **A**. This highly reactive intermediate could then react with appropriate nucleophiles and precede a cascade process. For example, with the application of functional molecules possessing both nucleophiles and leaving groups (Nu-LG), such as ylides or even another allylic nitro moiety, the above-mentioned strategy led to the formation of isoxazoline-N-oxide through an intramolecular SN_2 substitution.[2a] The successful one-pot synthesis of *NH*-1,2,3-triazole also suggested the similar reaction nature (Scheme 1C).[2b]

Notably, it has been reported in the literature that nucleophilic substitution of the allylic nitro group usually required harsh conditions (such as high temperature),[3] transition-metal assistance,[4] or strong Lewis acid activation.[5] Thus, the effective substitution of allylic nitro group under mild

(1) (a) Sun, X.; Sengupta, S.; Petersen, J. L.; Wang, H.; Lewis, J. P.; Shi, X. *Org. Lett.* **2007**, *9*, 4495–4498. (d) Zhong, C.; Chen, Y.; Petersen, J. L.; Akhmedov, N.; Shi, X. *Angew. Chem., Int. Ed.* **2009**, *48*, 1279–1282. (c) Chen, Y.; Zhong, C.; Sun, X.; Akhmedov, N.; Petersen, J. L.; Shi, X. *Chem. Commun.* **2009**, 5150–5152.

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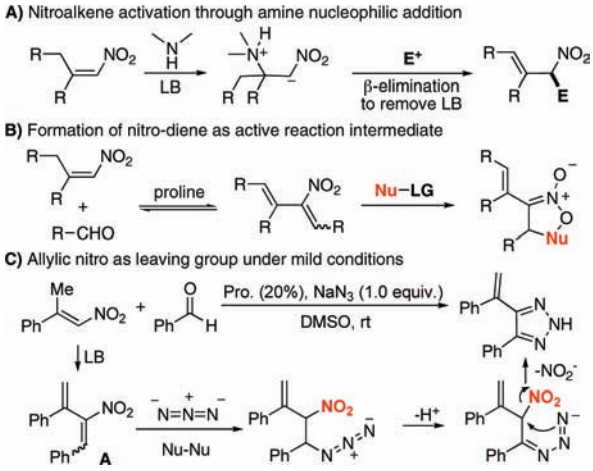
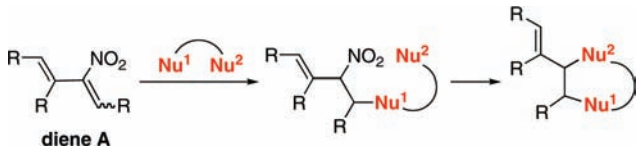
Scheme 1. Amine Activation of Nitroalkene in Cascade Process



conditions in our previous studies provided an appealing approach to further extend the cascade strategy for the stereoselective synthesis of complex building blocks. Combining these mechanistic discoveries, we postulated that the treatment of reactants with "di-nucleophile" moieties to the nitro-diene intermediate **A** could lead to the facile synthesis of complex functionalized cyclic molecules in a "one-pot" fashion (Scheme 2). Herein, we report the proline catalyzed

Scheme 2. Proposed "Di-nucleophile" Addition to Nitro Diene

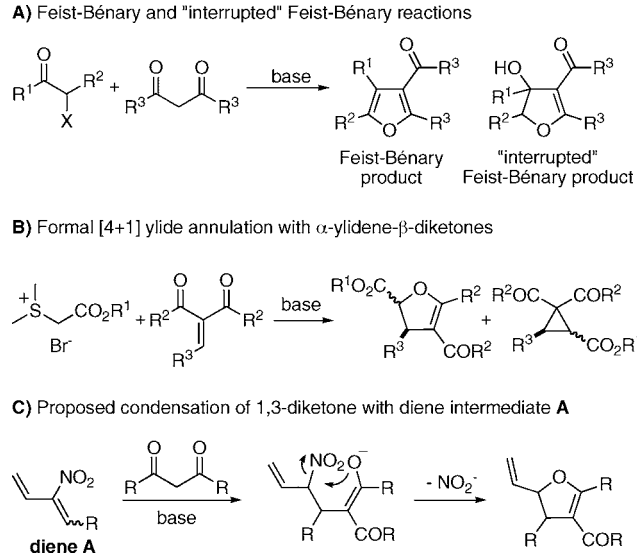


three-component condensation of nitroalkene, aldehyde and 1,3-dicarbonyl compound for the synthesis of substituted dihydrofurans with large substrate scope, good yields, and excellent diastereoselectivity.

Furans and their derivatives are an important class of compounds in chemical and biological research.[6] One of the most well-known approaches for the synthesis of substituted furan is the Feist-Bénary reaction, back to one century ago (Scheme 3A)[7] and the recent modified "interrupted" Feist-Bénary reaction.[8] Meanwhile, several methods were also reported focusing on the feasible cascade process to reach substituted dihydrofuran products with carbon substituents.[9]

More recently, Tang and co-workers[10] had reported an enantioselective synthesis of dihydrofurans via formal

Scheme 3. Synthesis of Dihydrofuran



[4 + 1] ylide annulation with excellent yields and enantioselectivity, although the substrate scope was limited (Scheme 3B). Previous studies by Ma,[11a] Liang,[11b] and Piras[11c] revealed the challenges in *cis/trans* diastereoselectivity and the competitive undesired cyclopropanation by products. Moreover, these methods usually needed rather specific α-ylidene-*β*-diketones and ylide auxiliaries, most of which were not readily available and had inevitably lowered the overall atom efficiency. Therefore, there is a strong desire for new synthetic methods that allow the easy preparation of dihydrofurans (DHF) with high atom efficiency and, more importantly, good feasibility to assemble various substitution patterns. Encouraged by our previous success, we envisioned that 1,3-dicarbonyl compounds could be one of the feasible dinucleophiles to react with the nitro-diene **A** and give the desired carbon-substituted dihydrofuran with different substitution patterns and high efficiency (Scheme 3C).

To test our hypothesis, reactions between nitroalkene **1a**, aldehyde **2a**, and cyclohexane-1,3-dione **3a** were investigated

(3) Barlaam, B.; Boivin, J.; Zard, S. Z. *Tetrahedron Lett.* **1990**, *31*, 7429–7432.

(4) For selected examples, see: (a) Tamura, R.; Hegedus, L. S. *J. Am. Chem. Soc.* **1982**, *104*, 3727–3729. (b) Ono, N.; Hamamoto, I.; Kaji, A. *J. Chem. Soc., Chem. Commun.* **1982**, 821. (c) Tamura, R.; Kai, Y.; Kakihana, M.; Hayashi, K.; Tsuji, M.; Nakamura, T.; Oda, D. *J. Org. Chem.* **1986**, *51*, 4375–4385.

(5) For selected examples, see: (a) Miyake, H.; Yamamura, K. *Tetrahedron Lett.* **1986**, *27*, 3025–3028. (b) Ono, N.; Kamimura, A.; Sasatani, H.; Kaji, A. *J. Org. Chem.* **1987**, *52*, 4133–4135.

(6) (a) Figadère, B. *Acc. Chem. Res.* **1995**, *28*, 359–365. (b) Roy, A.; Saraf, S. *Biol. Pharm. Bull.* **2006**, *29*, 191–201.

(7) (a) Feist, F. *Chem. Ber.* **1902**, *35*, 1537–1544. (b) Bénary, E. *Chem. Ber.* **1911**, *44*, 489–492.

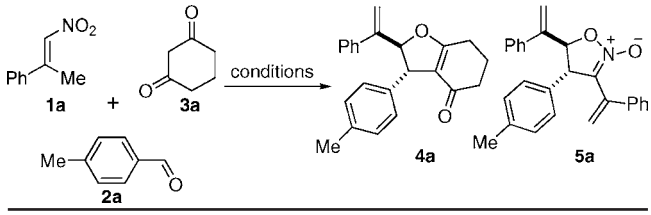
(8) For recent examples, see: (a) Calter, M. A.; Zhu, C. *Org. Lett.* **2002**, *4*, 205–208. (b) Calter, M. A.; Phillips, R. M.; Flaschenriem, C. *J. Am. Chem. Soc.* **2005**, *127*, 14566–14567.

(9) For recent examples, see: (a) Zhang, Y.; Raines, A. J.; Flowers, R. A., II *Org. Lett.* **2003**, *5*, 2363–2365. (b) Shen, R.; Huang, X. *Org. Lett.* **2008**, *10*, 3283–3286. (c) Wang, G.-W.; Dong, Y.-W.; Wu, P.; Yuan, T.-T.; Shen, Y.-B. *J. Org. Chem.* **2008**, *73*, 7088–7095. (d) Shen, R.; Zhu, S.; Huang, X. *J. Org. Chem.* **2009**, *74*, 4118–4123. (e) Wang, Q.-F.; Hou, H.; Hui, L.; Yan, C.-G. *J. Org. Chem.* **2009**, *74*, 7403–7406.

(10) (a) Zheng, J.-C.; Zhu, Y.-C.; Sun, X.-L.; Tang, Y.; Dai, L.-X. *J. Org. Chem.* **2008**, *73*, 6909–6912. For the first example of dihydrofuran synthesis via sulfur ylide, see: (b) Payne, G. B. *J. Org. Chem.* **1967**, *35*, 3351–3355.

(11) (a) Jiang, Y.; Ma, D. *Tetrahedron: Asymmetry* **2002**, *13*, 1033–1038. (b) Yang, Z.; Fan, M.; Mu, R.; Liu, W.; Liang, Y. *Tetradedron* **2005**, *61*, 9140–9146. (c) Bernard, A. M.; Frongia, A.; Piras, P. P.; Secci, F.; Spiga, M. *Org. Lett.* **2005**, *7*, 4565–4568.

Table 1. Reaction Condition Optimization[a]



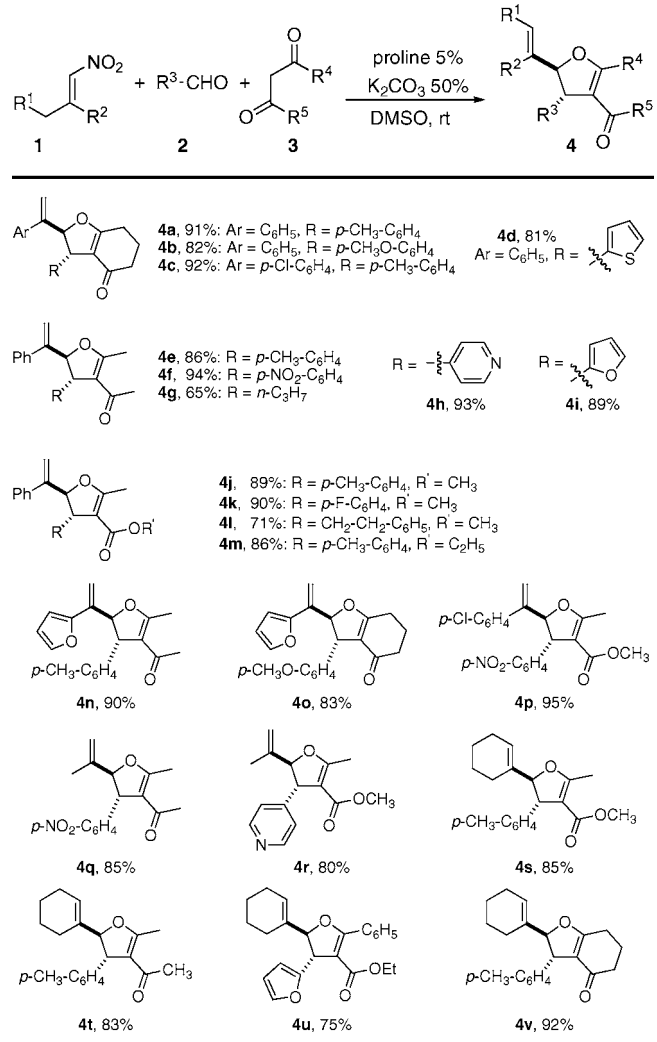
	cat.	base (equiv)	solv	time (h)	convn[b] (%)	yield (%)[c] 4a	5a
1	Proline (20%)	–	DMSO	2	77	30	1
2	Proline (20%)	K_2CO_3 (1.0)	DMSO	2	100	71[d]	8
3	–	K_2CO_3 (1.0)	DMSO	2	90	22	<5
4	Proline (20%)	K_2CO_3 (0.5)	DMSO	2	100	80[d]	<5
5	Proline (10%)	K_2CO_3 (0.5)	DMSO	3	100	87[d]	<5
6	Proline (5%)	K_2CO_3 (0.5)	DMSO	4	100	87[d]	<5
7	Proline (2%)	K_2CO_3 (0.5)	DMSO	8	100	74[d]	<5
8	**Proline (5%)**	**K_2CO_3 (0.5)**	**DMSO**	**4**	**100**	**91**[e]	**<5**
9	Proline (5%)	other bases[f]	DMSO	4	100	<85[e]	<5
10	Proline (5%)	K_2CO_3 (0.5)	solvents[g]	4	100	<72[e]	<5
11	PPh_3 (20%)	K_2CO_3 (0.5)	DMSO	3	100	26	18
12	Et_3N (20%)	K_2CO_3 (0.5)	DMSO	8	100	37	<5
13	DMAP (20%)	K_2CO_3 (0.5)	DMSO	8	100	30	21
14	Glycine (5%)	K_2CO_3 (0.5)	DMSO	4	100	69[e]	<5

[a] **1a:2a:3a** = 1:1:1, concentration of **2a** is 0.15 M; yields determined by NMR with 1,3,5-trimethoxybenzene as internal standard. [b] Based on the nitroalkene **1a**. [c] NMR yield with 1,3,5-trimethoxybenzene as internal standard. [d] Isolated yields. [e] Isolated yield based on aldehyde, with the laoding of **1a:2a:3a** = 1.2:1.0:1.1, concentration of **2a** is 0.15 M. [f] Other bases include Cs_2CO_3, NaOAc, NaO*t*Bu, Et_3N and DIPEA. [g] Solvents include DCM, EtOAc, Acetone, Toluene and THF. See Supporting Information for detailed condition screening.

(Table 1). The competing side reactions for this three-component condensation included the formation of isoxazoline **5a** and nitroalkene polymerization. To our delight, the desired DHF **4a** was formed when treating the three starting materials with proline, though the yield was low (30%, entry 1). Significant nitroalkene polymerization was observed in this case. Since one equivalent of HNO_2 would be generated in this process, various bases were added to balance the acidity of the overall reaction. With the application of 1.0 equiv of K_2CO_3, the yield of DHF was significantly improved (71%, entry 2). Notably, a much significantly lower yield was received when only K_2CO_3 was applied (22%, entry 3). These results were consistent with our previously reported proline-nitroalkene activation mechanism. Considering that strong basic conditions usually favored the undesired nitroalkene polymerization, the amount of K_2CO_3 was reduced to 0.5 equiv. Higher yield of **4a** was received as expected (80%, entry 4). Interestingly, decreasing the loading of proline resulted in better performance with only a slight increase in reaction time (entries 5−7). This could be explained by the relatively slower nitroalkene polymerization associated with the lower Lewis base loading. With this optimal condition, excellent yield of DHF **4a** was received as the single *trans* isomer, when slightly excess amounts (1.2 equiv) of nitroalkenes was applied (91%, entry 8). Different bases (such as DIPEA, Et_3N, and Cs_2CO_3) and various solvents have also been investigated (see detailed screening conditions in Supporting Information), and K_2CO_3 (0.5 equiv) in DMSO was confirmed as the optimal choice. Different Lewis base catalysts, such as PPh_3 and DMAP, have also been applied to catalyze this reaction. However, much lower yields were obtained (entries 11−13) along with the formation of significant amounts of **5a**. These results highlighted the unique reaction nature of proline catalyzed nitroalkene activation in cascade syntheses.

In addition, no *cis* diastereo isomers or cyclopropanation products were observed. The competing side reaction, homoisoxazoline-N-oxide formation, was also successfully diminished. Various nitroalkenes, aldehydes and 1,3-diketones/β-keto-esters were then applied to investigate the reaction substrate scope. The results are shown in Scheme 4.

Scheme 4. Substrate Scope of the One-Pot Dihydrofuran Synthesis[a]



[a] **1a:2a:3a** = 1.2:1.0:1.1, concentration of **2a** is 0.15 M; yields are isolated yields; only *trans* isomers were oberserved.

This new method worked for a great variety of substrates, giving the desired *trans* DHF in good to excellent yields. Both aromatic nitroalkene and aliphatic nitroalkene were suitable for this transformation, giving good diversity on the

C-5 position. Meanwhile, the allylic ether functionality was introduced, providing a new "synthetic handle" to the product. A large group of different aldehydes, including aromatic (with either electron donating groups or electron withdrawing groups), aliphatic and heterocyclic structures, were all suitable for this reaction, which provided an efficient strategy to introduce different carbon-substitute groups on the C-4 position. The efficient assembly of readily available diverse groups on the C-4 and C-5 position made the reported method highly efficient for the preparation of functional substituted DHF that would be challenging to reach via other methods. The application of different 1,3-diketone and β-keto-esters further extended this method for easy introduction of various functional groups on C-2 and C-3 positions. In the case of β-keto-esters, good chemoselectivity was achieved, giving only the ketone cyclization products. This result gave advantage to selectively introduce different groups on either C-2 or C-3 positions through the reaction with corresponding dinucleophiles (i.e., **4u**). Notably, excellent diastereoselectivity was achieved in all cases, while only *trans* isomers were observed. Thus, with the great diversity, high efficiency and excellent diastereoselectivity, this reported method could be applied as a new general protocol for the synthesis of various functional dihydrofuran building blocks.

In conclusion, a highly efficient cascade synthesis of dihydrofurans was developed through a proline catalyzed, one-pot three-component condensation of nitro alkenes, aldehydes and 1,3-diketone/β-keto-esters. This reaction used readily available starting materials under mild conditions and gave the desired products in excellent yields,chemoselectivity, and diastereoselectivity. Substituted groups on all the four positions of furan could be readily controlled with the applications of corresponding starting materials. With the great atom efficiency and functional group tolerability, the reported methods would be of great interest for chemical and pharmaceutical researchers by providing a readily available compound library. In addition, the success of this method provided further strong support for the proposed secondary amine nucleophilic addition to nitroalkene. Further extension of this strategy with other plausible dinucleophiles for new transformations is being examined. An enantioselective version of DHF synthesis (<5% ee were observed with proline as catalyst in all cases) and application in natural product synthesis are also under investigation in our group.

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Supporting Information Available: Experimental details, spectrographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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