HETEROCYCLES, Vol. 97, No. 1, 2018, pp. 569 - 573. © 2018 The Japan Institute of Heterocyclic Chemistry
Received, 31st January, 2018, Accepted, 8th March, 2018, Published online, 15th March, 2018
DOI: 10.3987/COM-18-S(T)29

REACTIONS OF PYRUVATE-DERIVED DIHYDROPYRANS WITH FORMALDEHYDE: SYNTHESIS OF FUNCTIONALIZED FUROPYRANS AND RELATED PRODUCTS

Pandurang V. Chouthaiwale, Ravindra D. Aher, and Fujie Tanaka*

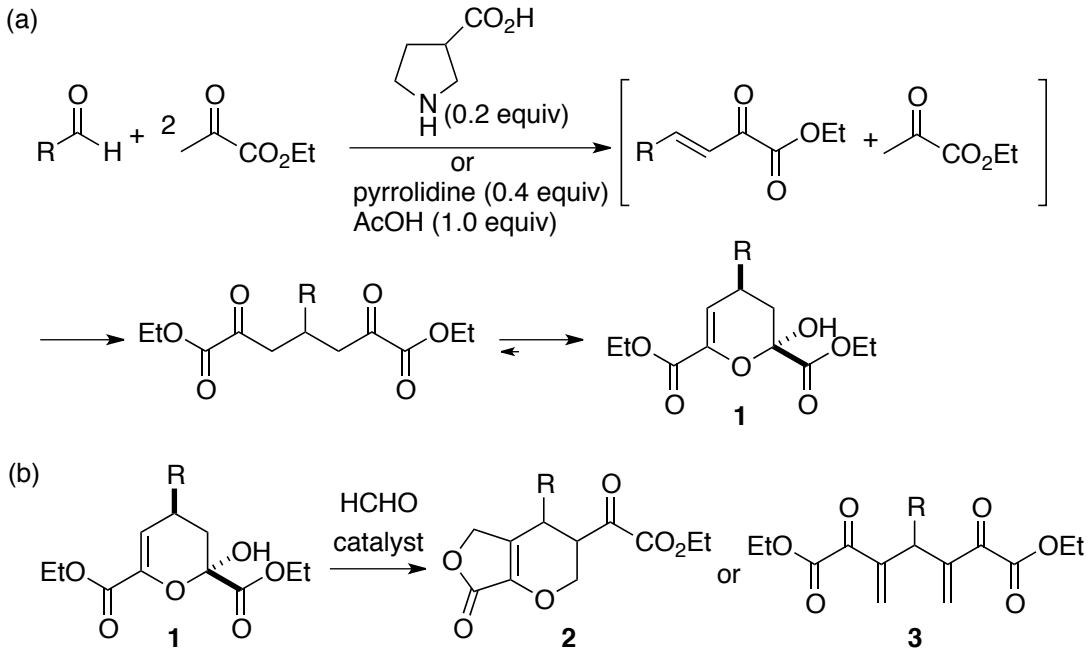
Chemistry and Chemical Bioengineering Unit, Okinawa Institute of Science and Technology Graduate University, 1919-1 Tancha, Onna, Okinawa 904-0495, Japan. E-mail: ftanaka@oist.jp

Abstract – Reactions that afford functionalized furopyrans and/or dimethylene derivatives from pyruvate-derived dihydropyrans and formaldehyde are described.

Construction of functionalized molecules is of interest in drug discovery and related areas.[1,2] Chemical transformations of molecules that act as both nucleophiles and electrophiles, such as pyruvates, are useful starting materials for the syntheses of functionalized molecules in short routes, however, the reactivities of the molecules must be controlled to lead to the desired products.[2,3] We have recently developed cascade reactions of pyruvates with aldehydes that afford functionalized dihydropyran derivatives **1** (Scheme 1a).[2,3] We have also demonstrated that the products, the dihydropyran derivatives, can be further transformed.[2,3] As part of our on-going effort to synthesize functionalized molecules, here we report the reactions between dihydropyran derivatives **1** and formaldehyde to afford furopyrans, diolefin derivatives, and related products (Scheme 1b). Depending on catalyst and conditions, either furopyrans or diolefin derivatives were obtained as the major products.

Pyruvates and pyruvate-derived molecules have enolizable ketone moieties and α-keto ester groups that act as nucleophiles and electrophiles, respectively. Tuning of the reactivities of these groups is necessary to obtain certain desired products. Therefore, first, catalysts and conditions were evaluated for selective formation of furopyran derivative **2**, dimethylene derivative **3**, and/or other products in the reaction of **1a** and formaldehyde (paraformaldehyde was used as the source of formaldehyde). Selected results are shown in Table 1. The reaction in the presence of pyrrolidine (0.5 equiv) and acetic acid (1.0 equiv) afforded furopyran derivative **2a** as the major product with **3a** as the minor product (entry 1). On the other hand, the reactions in the presence of diethylamine (0.25 equiv) and acetic acid (0.5

equiv) gave dimethylene derivative **3a** as the major product (entries 8 and 9). The use of higher loading of diethylamine also led to the formation of **3a** as the major product (entry 10). Formation of pyran derivative **4a** was observed under certain conditions.

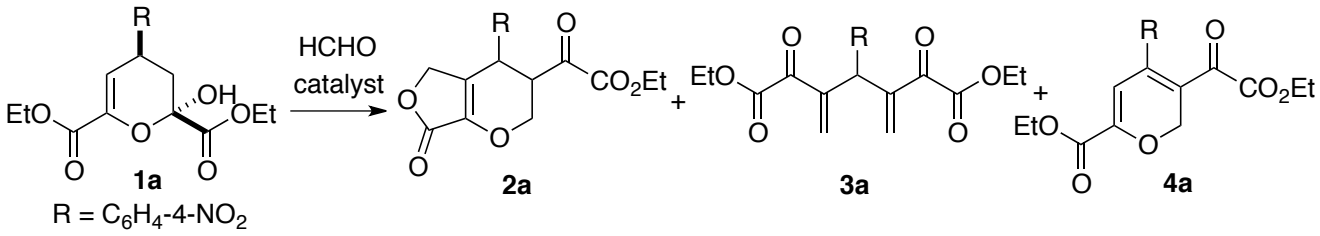


Scheme 1. (a) Our previous synthesis of functionalized dihydropyran derivatives **1** from pyruvate with aldehydes.[2,3] (b) Reaction of **1** with formaldehyde to afford furopyran derivatives **2** or dimethylene derivatives **3**.

Next, catalyst systems pyrrolidine-acetic acid and diethylamine-acetic acid were used to synthesize various **2** and **3**, respectively (Tables 2 and 3). Under the pyrrolidine-acetic acid catalysis conditions, furopyran derivatives **2b**-**2d** were formed as the major products (Table 2). In the reactions affording **2**, formation of **3** was also observed as the minor product. For the formation of **2a**, **2b**, and **2c**, single isomers were obtained. With the use of the diethylamine-acetic acid catalyst system, dimethylene derivatives **3** were obtained (Table 3). For the reactions affording **3b**-**3e** under the diethylamine-acetic acid catalyst system, formation of pyran derivatives (such as **4a** formed in the reaction of **1a**) was not observed. With the use of increased loading of diethylamine, dimethylene derivatives **3** were obtained in high yield in 12-14 h.

Plausible pathways for the formation of **2** and **4** are shown in Scheme 2. For the formation of **2** and **3**, two formaldehyde molecules reacted with one molecule of **1**. For the formation of **4a**, however, only one formaldehyde molecule reacted with one molecule of **1**. For the formation of **2**, aldol reaction, aldol condensation to generate the methylene group, lactonization, and oxa-Michael addition may be involved; formation of **2** is a cascade reaction.[4]

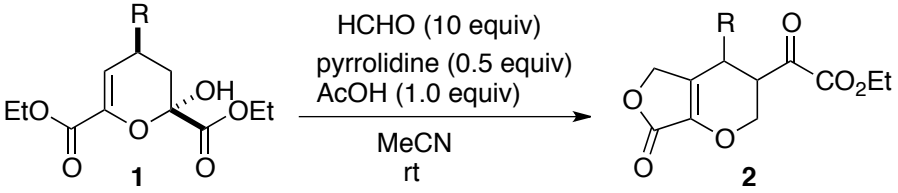
Table 1. Catalyst evaluations of the reaction of **1a** with formaldehyde[a]

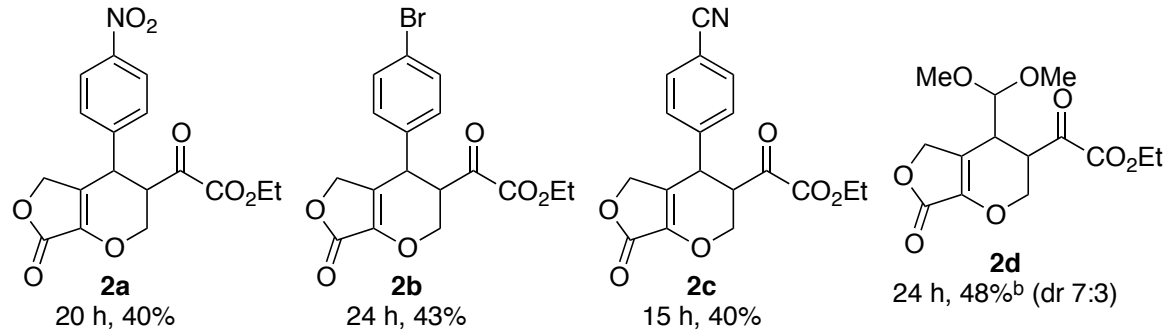


entry	catalyst	products (yield, %) or ratio of products
1	pyrrolidine (0.5 equiv)-AcOH (1.0 equiv)	**2a** (40%), **3a** (22%)
2	pyrrolidine (0.5 equiv)-AcOH (0.5 equiv)	**2a**:**3a** = 1:3[b]
3	pyrrolidine (0.5 equiv)-AcOH (2.0 equiv)	**2a** (25%), **3a** (20%), **4a** (5%)
4	pyrrolidine (0.5 equiv)-CF_3CO_2H (1.0 equiv)	no product derived from **1**
5	pyrrolidine (0.5 equiv)-4-nitrobenzoic acid (1.0 equiv)	**2a**:**3a** = 1:2[b]
6	pyrrolidine (0.5 equiv)-4-nitrobenzoic acid (0.5 equiv)	**2a**:**3a** = 1:3[b]
7[c]	pyrrolidine (0.5 equiv)	**3a** (10%), **4a** (14%)
8[d]	Et_2NH (0.25 equiv)-AcOH (0.5 equiv)	**3a** (60%)
9[c]	Et_2NH (0.25 equiv)-AcOH (0.5 equiv)	**3a** (49%), **4a** (24%)
10[e]	Et_2NH (0.7 equiv)-AcOH (0.5 equiv)	**3a** (40%), **4a** (20%)
11[c]	Et_2NH (0.25 equiv)	**3a** (39%), **4a** (25%)
12[c]	AcOH (1.0 equiv)	no product derived from **1**

[a] Conditions: compound **1** (0.1 mmol, 1.0 equiv), paraformaldehyde (1.0 mmol, 10 equiv), and catalyst in MeCN (0.3 mL) at rt (25 °C) for 24 h. [b] Determined by ^{1}H NMR analysis. [c] MeCN (1.0 mL). [d] MeCN (0.5 mL). [e] A 2.7 mmol-scale (compound **1**) reaction, MeCN (27 mL).

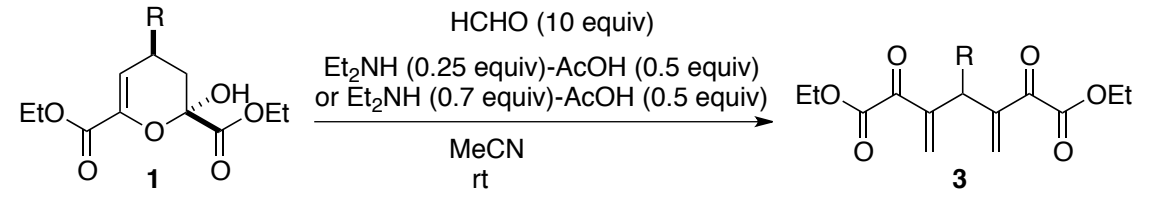
Table 2. Synthesis of furopyran derivatives **2**[a]

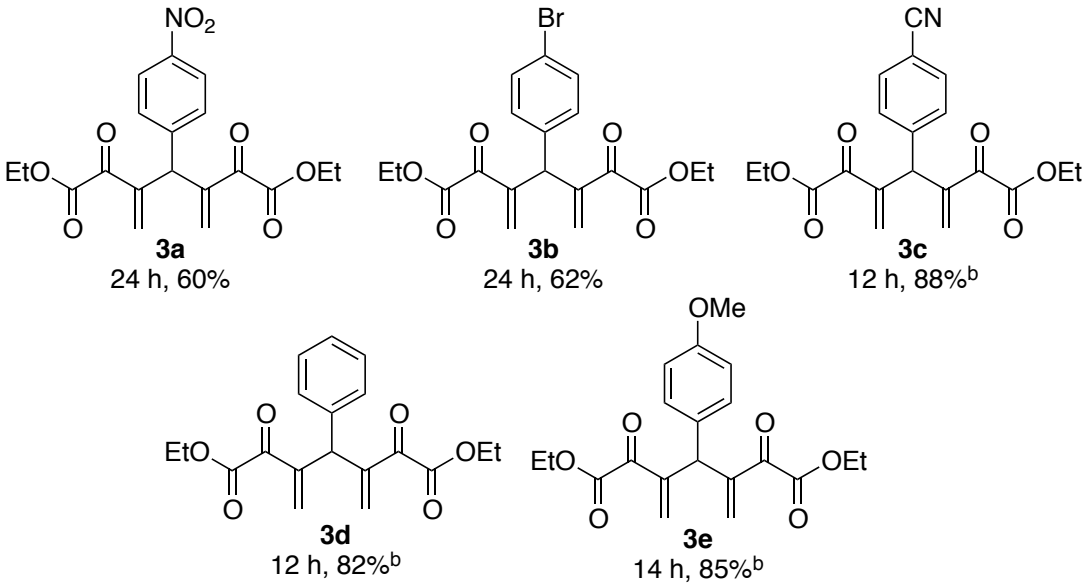




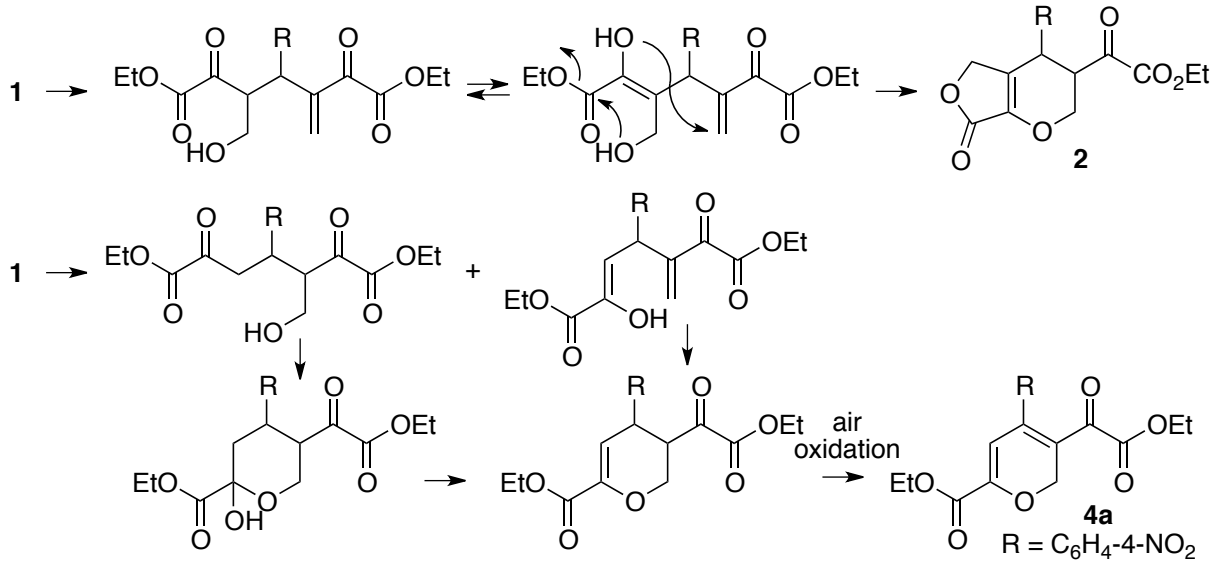
[a] Conditions: Compound **1** (0.1 mmol), paraformaldehyde (1.0 mmol), pyrrolidine (0.05 mmol), and AcOH (0.1 mmol) in MeCN (0.3 mL). [b] Compound **1** (0.1 mmol), paraformaldehyde (1.0 mmol), pyrrolidine (0.025 mmol), and AcOH (0.1 mmol) in MeCN (0.3 mL).

Table 3. Synthesis of dimethylene derivatives **3**[a]





[a] Conditions: Compound **1** (0.1 mmol), paraformaldehyde (1.0 mmol), Et_2NH (0.025 mmol), and AcOH (0.05 mmol) in MeCN (0.5 mL). [b] Conditions: Compound **1** (0.2 mmol), paraformaldehyde (2.0 mmol), Et_2NH_2 (0.14 mmol), and AcOH (0.1 mmol) in MeCN (2.0 mL).



Scheme 2. Plausible pathways for the formation of **2** and **4a**

The furopyran core structure present in **2** is found in natural products, such as cephalosol,[5] distomadines,[6] and patulin isomers.[7] Synthesis of furopyrans has been of interest.[8] Diolefins **3** have enone functionalities and may be transformed further to various functional molecules.

In summary, we have developed reactions of dihydropyran derivatives derived from pyruvates that afford furopyran derivatives and dimethylene derivatives, respectively, depending on catalyst conditions.

ACKNOWLEDGEMENTS

We thank Dr. Michael Chandro Roy, Research Support Division, Okinawa Institute of Science and Technology Graduate University for mass analyses. This study was supported by the Okinawa Institute of Science and Technology Graduate University.

Supporting Information Available: Experimental procedures, product characterization, and NMR spectra.

REFERENCES AND NOTES

1. T. E. Nielsen and S. L. Schreiber, *Angew. Chem. Int. Ed.*, 2007, **47**, 48 and references cited therein.
2. P. V. Chouthaiwale and F. Tanaka, *Chem. Commun.*, 2014, **50**, 14881.
3. P. V. Chouthaiwale, S. Lapointe, and F. Tanaka, *Heterocycles*, 2017, **95**, 587.
4. C. M. R. Volla, I. Atodiresei, and M. Rueping, *Chem. Rev.*, 2014, **114**, 2390 and references cited therein.
5. H. W. Zhang, W. Y. Huang, J. R. Chen, W. Z. Yan, D. Q. Xie, and R. X. Tan, *Chem. Eur. J.*, 2008, **14**, 10670.
6. A. E. R. Jolibois, W. Lewis, and C. J. Moody, *Org. Lett.*, 2014, **16**, 1064.
7. B. Puetzer, C. H. Nield, and R. H. Barry, *Science*, 1945, **101**, 307.
8. S. Jin, C. Jiang, X. Peng, C. Shan, S. Cui, Y. Niu, Y. Liu, Y. Lan, Y. Liu, and M. Cheng, *Org. Lett.*, 2016, **18**, 680; Y. Liu, S. Jin, Y. Wang, S. Cui, X. Peng, Y. Niu, C. Du, and M. Cheng, *Chem. Commun.*, 2016, **52**, 6233; Y. Abdi, B. Boutemeur-Kheddis, M. Hamdi, O. Talhi, F. A. A. Paz, G. Kirsch, and A. M. S. Silva, *Synlett*, 2015, **26**, 1749; S.-Y. Meng, Y.-K. Jia, M. Li, W.-W. Han, F.-Q. Wang, S.-Q. Zhu, S.-S. Qin, H.-Y. Song, Y. Hou, X.-F. Shi, F.-W. Liu, and H.-M. Liu, *Tetrahedron*, 2015, **71**, 9420.