Pergamon

Tetrahedron Letters 41 (2000) 3299–3302

TETRAHEDRON LETTERS

Synthesis of 5,6-dihydro-4-hydroxy-2-pyrones via formal cycloaddition reactions

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Received 8 December 1999; revised 3 March 2000; accepted 7 March 2000

Abstract

Synthesis of functionalized 5,6-dihydro-4-hydroxy-2-pyrones via a novel formal cycloaddition reaction between electron-deficient aldehydes and pyrandione **2** is described. Pericyclic and aldol-like pathways have been proposed.

The 5,6-dihydro-4-hydroxy-2-pyrone ring is contained within a number of natural products, such as mescengricin, a neuronal cell protecting substance.[1] It is also the pharmacophore of a promising series of nonpeptidic HIV protease inhibitors.[2] A number of methods for the synthesis of this structure have appeared in the literature.[2,3] In this report, we wish to describe a novel formal cycloaddition reaction followed by decarboxylation that leads to the formation of the dihydropyrone functionality.

During the course of our investigation of asterriquinone analogs, we required a convergent route for the synthesis of structure **3**. It has been reported by Steglich and co-workers in their synthesis of grevilline that structure **3** can be readily obtained through condensation of aromatic aldehyde **1** and pyrandione **2**.[4] Following the reported procedure, benzaldehyde **1** (Ar=phenyl) was reacted with pyrandione **2** (acetic acid, catalytic HCl, 90°C, 3 h) to give the desired product **3** (Ar=phenyl) in 90% yield (Scheme 1). However, when 3-pyridinecarboxaldehyde was reacted with **2** under the same reaction conditions, no aldol product **3** was obtained. Instead, dihydropyrone **4** (Ar=3-pyridyl) was isolated in 75% yield.

We rationalize this unexpected transformation to proceed through two potentially competing mechanistic pathways as outlined in Scheme 2. Under the reaction conditions, pyrandione **2** exists in equilibrium with its enol form **5**. Protonation of the basic nitrogen atom of 3-pyridinecarboxaldehyde generates **6**, which is a very electron-deficient aldehyde. The ability of aldehydes bearing strongly electrophilic α-substituents to function as heterodienophiles has been known for some time.[5] A pericyclic pathway has been proposed in the reaction of 1-methoxy-3-[(trimethylsilyl)oxy]-butadiene ('Danishefsky diene') with aldehydes under Lewis acid catalysis.[6] In close analogy, the electron-rich diene **5** could undergo [4+2] cycloaddition with the electron-deficient aldehyde **6** to produce the bicyclic adduct **7** (path A). Decarboxylation of **7** provides **9** which, after isomerization, affords the final product **4a**.

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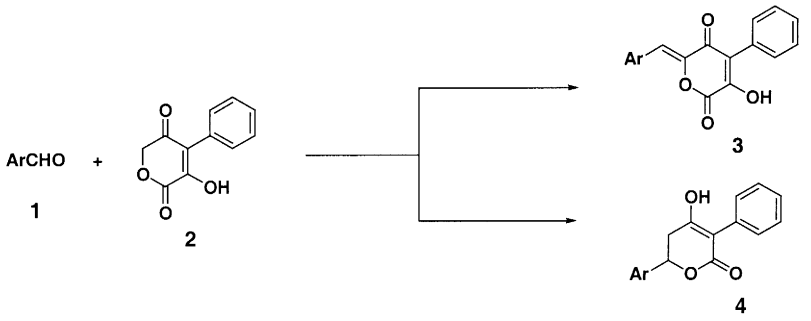
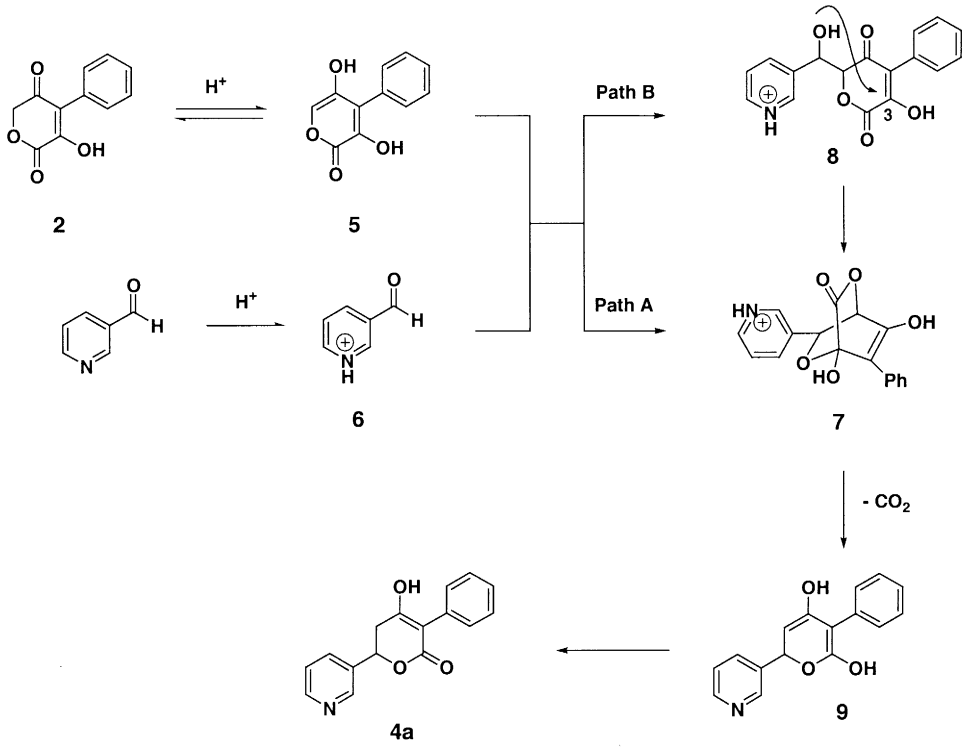
0040-4039/00/$ - see front matter
PII: S0040-4039(00)00422-6



Scheme 1.

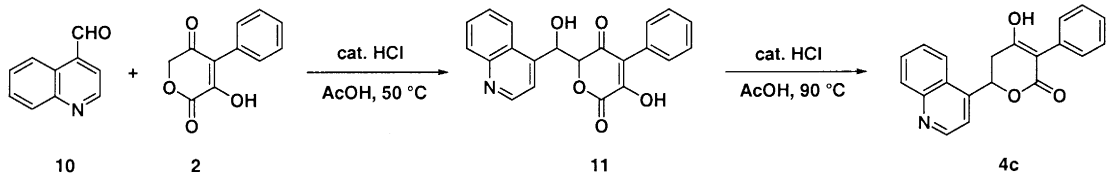


Scheme 2.

Alternatively, the aldol condensation can serve to join the two reactants **5** and **6** to produce intermediate **8** (path B). Due to the cationic character in the transition state of the dehydration process, the protonated pyridyl moiety of **8** significantly increases the transition state energy of the dehydration step. Instead of losing one molecule of water to form structure **3**, as in the case of benzaldehyde, intermediate **8** allows the newly formed hydroxyl group to attack the 3-carbon position to produce the bicyclic product **7**, which, after collapse, affords **4**. In a closely related case, Corey found that the reaction of Danishefsky diene with aldehydes in the presence of the tryptophan-derived oxazaborolidine catalyst proceeded through a two-step aldol-Michael sequence.[7]

In order to differentiate the two reaction pathways, we tried to isolate the proposed aldol intermediate and to see if we can independently transform it into the corresponding dihydropyrone. When 4-quinolinecarboxaldehyde **10** was allowed to react with pyrandione **2** at lower reaction temperature (50°C, 1.5 h), the carbinol **11** precipitated out during the reaction and was isolated by filtration in 75% yield

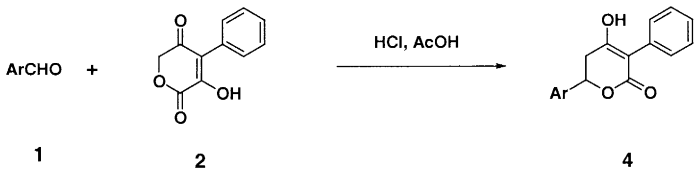
(Scheme 3).[8] Indeed, when carbinol **11** was subjected to the same reaction conditions (acetic acid, catalytic HCl, 90°C, 3 h), dihydropyrone **4c** was generated in 90% yield. This observation strongly supports the two-stage aldol pathway.

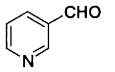
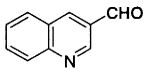
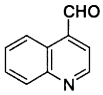
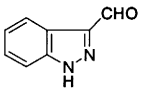
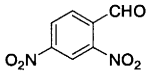


Scheme 3.

To demonstrate the generality of this reaction, and because of the relevance to certain synthetic targets of interest to us, we have examined reactions between pyrandione **2** and a variety of electron-deficient aldehydes. Selected results from these investigations are shown in Table 1.[9]

Table 1



Entry	ArCHO	Isolated Yield of 4 (%)
a		75
b		72
c		70
d		80
e		86
f		62
g		45

In a typical experiment, pyrandione **2** (1.0 mmol) and an aldehyde (1.0 mmol) are dissolved in glacial acetic acid (5.0 mL). To this solution is added three drops of concentrated HCl via a pipet. The reaction mixture is heated at 90°C under stirring for 3 h. After cooling to room temperature, Et_2O (10 mL) is added. The precipitate is collected by filtration. Further purification by recrystallization or chromatography affords the final product.

Acknowledgements

We are grateful to Ms. Amy Bernick for performing mass spectral analysis. We also thank Drs. Zhiguo Song and Lushi Tan of the Merck Process Department for helpful discussions. Dr. A. Brian Jones is acknowledged for his advice and a critical reading of the manuscript.

References

1. Kim, J.; Shin-ya, K.; Furihata, K.; Hayakawa, Y.; Seto, H. *Tetrahedron Lett.* **1997**, *38*, 3431.
2. Thaisrivongs, S.; Romero, D. L.; Tommasi, R. A.; Jarakiraman, M. N.; Strohbach, J. W.; Turner, S. R.; Biles, C.; Morge, R. R.; Jonhson, P. D.; Aristoff, P. A.; Tomich, P. K.; Lynn, J. C.; Horng, M.; Chong, K.-T.; Hinshaw, R. R.; Howe, W. J.; Finzel, B. C.; Watenpaugh, K. D. *J. Med. Chem.* **1996**, *39*, 4630.
3. (a) Tanabe, Y.; Miyakado, M.; Ohno, N.; Yoshioka, H. *Chem. Lett.* **1982**, 1543. (b) Glein, S.; Glein, R. *Bull. Soc. Chim., Fr.* **1968**, 288. (c) Landi, J. J. J.; Garofalo, L. M.; Ramig, K.; *Tetrahedron Lett.* **1993**, 34, 277. (d) Kawakami, H.; Hirokawa, S.; Asaoka, M.; Takei, H. *Chem. Lett.* **1987**, 85.
4. (a) Lohrisch, H.; Schmidt, H.; Steglich, W. *Liebigs Ann. Chem.* **1986**, 195. (b) Lohrisch, H.; Kopanski, L.; Herrmann, R.; Schmidt, H.; Steglich, W. *Liebigs Ann. Chem.* **1986**, 177.
5. (a) Weinreb, S. N.; Staib, R. R. *Tetrahedron* **1982**, *38*, 3087. (b) Boger, D. L.; Weinreb, S. N. In *Hetero Diels–Alder Methodology in Organic Synthesis*; Wasserman, H. H., Ed.; Academic Press; San Diego, CA, 1987; Vol. 47.
6. Danishefsky, S. J.; Larson, E.; Askin, D.; Kato, N. *J. Am. Chem. Soc.* **1985**, *107*, 1246.
7. Corey, E. J.; Cywin, C. L.; Roper, T. D. *Tetrahedron Lett.* **1992**, *33*, 6907.
8. Carbinol **11** was formed as a single diastereomer, whose relative configuration has not yet been determined. Compound **11**: MS (ESI) *m/z* 362 (M+1); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.27 (d, J=5.3 Hz, 1H), 8.34 (d, J=8.4 Hz, 1H), 8.29 (d, J=8.5 Hz, 1H), 8.08 (t, J=8.4 Hz, 1H), 8.02 (d, J=5.0 Hz, 1H), 7.96 (t, J=8.4 Hz, 1H), 7.20 (m, 5H), 6.07 (s, 1H), 5.36 (s, 1H).
9. Compound **4a**: MS (ESI) *m/z* 268 (M+1); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.70 (m, 2H), 8.25 (d, J=7.5 Hz, 1H), 7.83 (dd, J=8.5, 7.5 Hz, 1H), 7.75 (d, J=7.2 Hz, 2H), 7.33 (t, J=7.2 Hz, 2H), 7.19 (m, 1H), 5.27 (dd, J=3.3, 7.1 Hz, 1H), 3.61 (dd, J=3.2, 14.3 Hz, 1H), 3.19 (dd, J=7.1, 14.3 Hz, 1H). Compound **4b**: MS (ESI) *m/z* 318 (M+1); ^{1}H NMR (400 MHz, acetone-d_6) δ 8.97 (d, J=2.2 Hz, 1H), 8.37 (s, br, 1H), 8.06 (d, J=8.1 Hz, 1H), 7.97 (d, J=8.1 Hz, 1H), 7.80 (d, J=7.2 Hz, 2H), 7.75 (t, J=8.0 Hz, 1H), 7.62 (t, J=8.0 Hz, 1H), 7.28 (t, J=7.2 Hz, 2H), 7.18 (m, 1H), 5.33 (dd, J=3.4, 7.0 Hz, 1H), 3.79 (dd, J=3.4, 14.3 Hz, 1H), 3.37 (dd, J=7.0, 14.3 Hz, 1H). Compound **4c**: MS (ESI) *m/z* 318 (M+1); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.18 (d, J=5.2 Hz, 1H), 8.66 (d, J=8.4 Hz, 1H), 8.26 (d, J=8.2 Hz, 1H), 8.08 (t, J=8.0 Hz, 1H), 7.82 (d, J=7.2 Hz, 2H), 7.34 (t, J=7.3 Hz, 2H), 7.20 (m, 1H), 5.41 (dd, J=3.0, 9.2 Hz, 1H), 4.25 (dd, J=3.0, 14.3 Hz, 1H), 3.63 (dd, J=9.3, 14.3 Hz, 1H). Compound **4d**: MS (ESI) *m/z* 257 (M+1); ^{1}H NMR (400 MHz, acetone-d_6) δ 8.92 (s, 1H), 7.99 (d, J=7.2 Hz, 1H), 7.53 (s, 1H), 7.32 (t, J=7.2 Hz, 1H), 7.18 (t, J=7.2 Hz, 1H), 5.21 (dd, J=3.7, 6.9 Hz, 1H), 3.64 (dd, J=3.4, 15.5 Hz, 1H), 3.34 (dd, J=6.6, 15.5 Hz, 1H). Compound **4e**: MS (ESI) *m/z* 307 (M+1); ^{1}H NMR (400 MHz, acetone-d_6) δ 8.08 (m, 2H), 7.98 (d, J=8.3 Hz, 1H), 7.68 (d, J=8.5 Hz, 1H), 7.54 (t, J=8.4 Hz, 1H), 7.35 (m, 2H), 7.29 (t, J=8.5 Hz, 1H), 7.24 (m, 1H), 5.40 (dd, J=4.1, 9.6 Hz, 1H), 3.98 (dd, J=4.2, 16.0 Hz, 1H), 3.44 (dd, J=9.6, 16.0 Hz, 1H). Compound **4f**: MS (ESI) *m/z* 357 (M+1); ^{1}H NMR (400 MHz, acetone-d_6) δ 7.82 (d, J=7.5 Hz, 2H), 7.30 (t, J=7.4 Hz, 2H), 7.27 (m, 1H), 5.22 (dd, J=3.5, 7.0 Hz, 1H), 3.62 (m, 1H), 3.28 (dd, J=7.0, 14.3 Hz, 1H). Compound **4g**: ^{1}H NMR (400 MHz, acetone-d_6) δ 8.74 (d, J=2.4 Hz, 1H), 8.51 (dd, J=2.4, 8.5 Hz, 1H), 7.99 (d, J=8.6 Hz, 1H), 7.89 (d, J=7.2 Hz, 2H), 7.32 (t, J=7.5 Hz, 2H), 7.20 (m, 1H), 5.31 (dd, J=3.8, 7.9 Hz, 1H), 4.06 (dd, J=3.8, 14.4 Hz, 1H), 3.56 (dd, J=7.9, 14.5 Hz, 1H).