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Scope and Diastereoselectivity of the "Interrupted" Feist–Bénary Reaction

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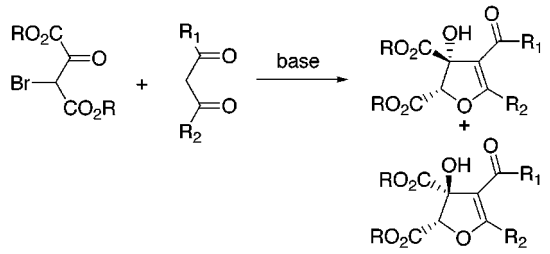
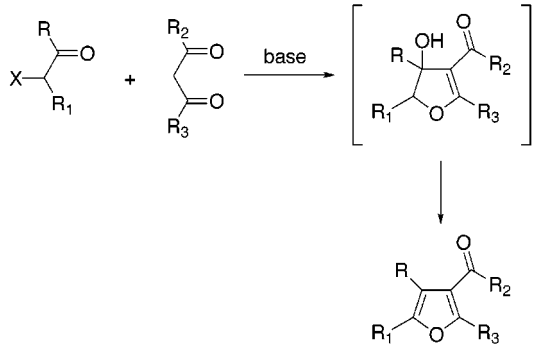
ABSTRACT



The base-promoted condensation of *β*-dicarbonyl compounds with α-haloketones, the Feist–Bénary reaction, conveniently produces highly substituted dihydrofurans. We show here that this reaction is quite general with respect to the nature of the *β*-dicarbonyl compound, proceeding with *β*-ketoesters, *β*-oxopropionates, *β*-diketones, and *β*-dialdehydes. We also show that the diastereoselectivity of this reaction depends on the acidity of the nucleophile.

In a search for convenient methods of preparation of highly oxidized intermediates for the synthesis of the zaragozic acids, we became aware of the Feist−Bénary reaction.[1] This reaction generally involved the base-promoted condensation of *β*-dicarbonyl compounds with α-haloketones to produce furans (Scheme 1). However, running the reaction under milder conditions allowed the isolation of a dihydrofuran intermediate. Several groups studied the mechanism and scope of this "interrupted" reaction,[2] and one group proposed a relative stereochemistry for the dihydrofuran.[2b] However, the diastereoselectivity of dihydrofuran formation had never been rigorously determined or explained, nor had the generality of this reaction with regard to dicarbonyl reactant been explored. Therefore, we undertook a study to address both of these issues.

Scheme 1



We initially employed α-bromooxaloacetates as electrophiles in combination with oxaloacetate nucleophiles (Scheme 2). We employed several conditions for this coupling. As reported in the literature, the commercially available sodium salt of diethyl oxaloacetate reacted with 0.5 equiv of bromine in ether to afford tetraesters **1a**,**b**.[2a] Similar treatment of the sodium salt of di-*tert*-butyl oxaloacetate,[3] formed in situ, afforded the corresponding dihydrofurans **2a**,**b** in moderate yield and diastereoselectivity. We achieved similar results using di-*tert*-butyl oxaloacetate in the presence of 1 equiv of triethylamine and 0.5 equiv of bromine.

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

(2) (a) Dunlop, A. P.; Hurd, C. D. *J. Org. Chem.* **1950**, *15*, 1160−1164. (b) Cantlon, I. J.; Cocker, W.; McMurry, T. B. H. *Tetrahedron* **1961**, *15*, 46−52.

(3) Heidelberger, C.; Hurlbert, R. B. *J. Am. Chem. Soc.* **1950**, *72*, 4704−4706.

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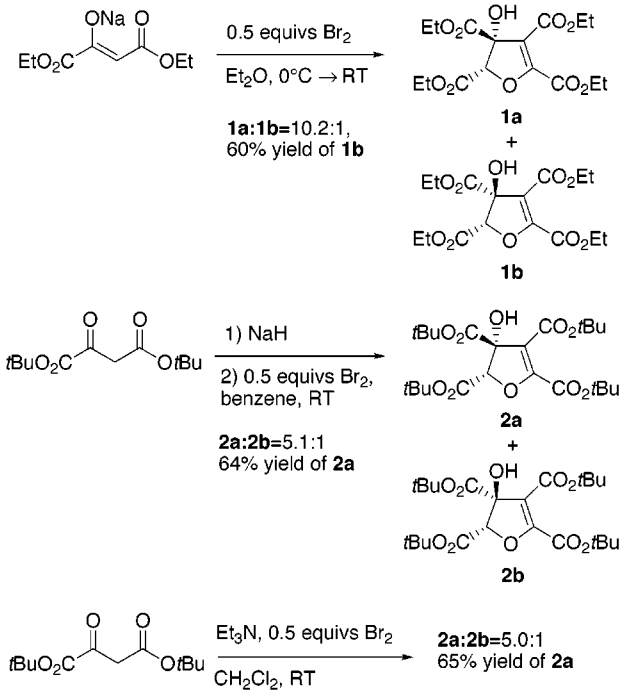
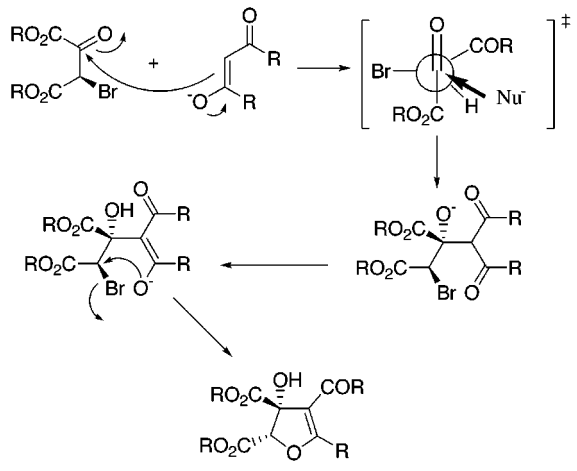
Scheme 2



Cantalon assumed that the major tetraethyl ester stereoisomer, **1a**, possessed the *cis* stereochemistry on the basis of thermodynamic arguments.[2b] We were able to obtain single crystals of **1a** suitable for X-ray crystallographic analysis and confirmed that this isomer did in fact possess the *cis* stereochemistry. By analogy and comparison of ^{1}H NMR spectra, we assigned the stereochemistry of **2a** as also being *cis*. We performed several control experiments to establish that the ratio of stereoisomers resulted from kinetic control. For example, treatment of either **2a** or **2b** with sodium methoxide, triethylamine, or DBU resulted in no interconversion.

We propose that the kinetic selectivity for the *cis*-dihydrofuran resulted from a diastereoselective aldol reaction

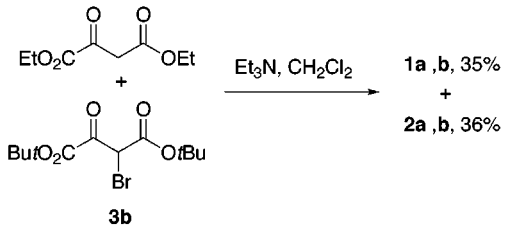
Scheme 3



of the enolate with the chiral α-bromoketone (Scheme 3). Such selectivity in additions to α-haloketones is well documented[4] and is rationalized by the electrostatic model of Nguyen.[5] After addition, rapid proton transfer steps followed by cyclization led to the observed major diastereomer. This proposed mechanism predicted that the diastereoselectivity could potentially erode if the rate of cyclization was lowered sufficiently relative to the rate of retroaldol reaction. This situation could arise if the pK_a of the nucleophile precursor was sufficiently low.

To explore the scope of the reaction, we attempted a cross-coupling reaction between a bromooxaloacetate and an oxaloacetate bearing different ester substituents (Scheme 4).

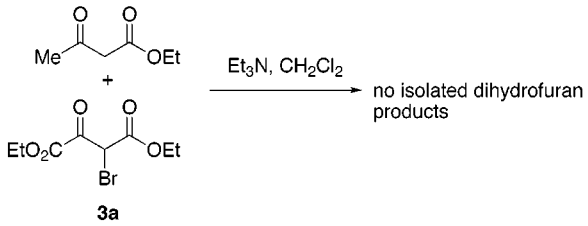
Scheme 4



The reaction of diethyl oxaloacetate with bromo-di-*tert*-butyl oxaloacetate (**3b**)[6] produced a mixture of dihydrofurans with all possible combinations of ester groups. This mixture probably resulted from bromine transfer from **3b** to the enolate of the dicarbonyl compound, generating a mixture of all possible bromooxaloacetates and oxaloacetates. Such a potential side reaction is likely to occur whenever the acidity of the dicarbonyl compound and the dehalogenated electrophile are similar.

We also attempted a cross-coupling reaction between a bromooxaloacetate and a simple *β*-ketoester (Scheme 5). This

Scheme 5



reaction did not produce any dihydrofuran products, again illustrating the difficulty of carrying out this coupling reaction

(4) Cornforth, J. W.; Conforth, R. H.; Mathew, K. K. *J. Chem. Soc.* **1959**, 2199−2204. For an example of an aldol addtion to a chiral α-chloroketone that gives similar selectivity, see: Yasuda, M.; Oh-hata, T.; Shibata, I.; Baba, A.; Matsuda, H.; Sonoda, N. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 1180−1186.

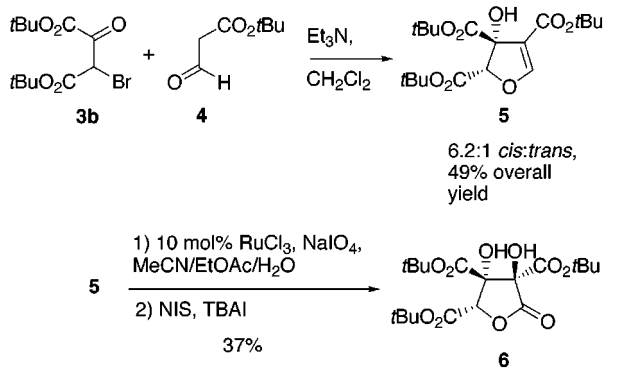
(5) Nguyen, T. A. *Top. Curr. Chem.* **1980**, 146−162.

(6) General procedure for the preparation of bromo-di-alkyl oxaloacetates: Conover, L. H.; Tarbell, D. S. *J. Am. Chem. Soc.* **1950**, *72*, 5221−5225.

with a β-dicarbonyl nucleophile having an acidity too close to that of the debrominated electrophile. Therefore, we turned to nucleophiles that were more acidic than β-ketoesters.

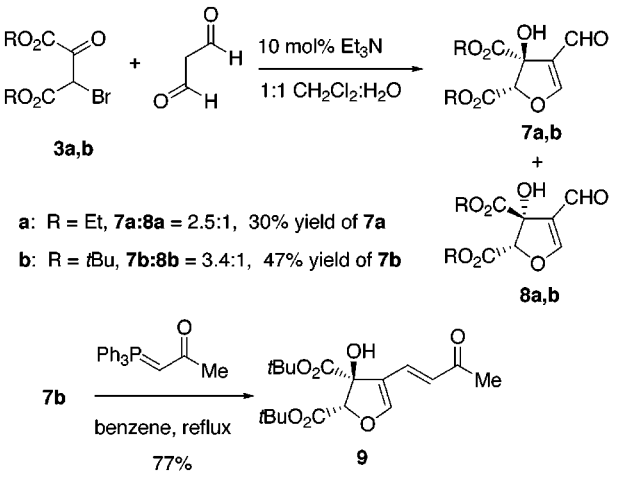
3-Oxopropionates functioned as suitable nucleophiles for the reaction with bromooxaloacetates (Scheme 6). Condensation of ester aldehyde **4**[7] with **3b** yielded dihydrofuran **5**. The stereochemistry of **5** was confirmed by X-ray crystallographic analysis of **6**, produced by dihydroxylation of **5** with RuO_4,[8] followed by lactol oxidation with *N*-iodosuccinimide (NIS) and tetrabutylammonium iodide (TBAI).[9]

Scheme 6



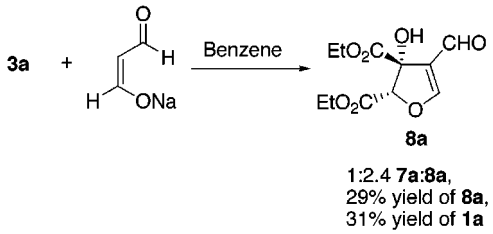
β-Dialdehydes also served as nucleophiles for the Feist−Bénary reaction (Scheme 7). Formation of an aqueous solution of malondialdehyde,[10] followed by condensation with bromooxaloacetates **3a**,**b**, yielded dihydrofurans **7a**,**b** and **8a**,**b**. However, in contrast to the reactions involving all previous nucleophiles, these condensations afforded the *trans* stereoisomer with low selectivity. The stereochemistry of **7b** was confirmed by conversion into enone **9** and X-ray crystallographic analysis of this compound.

Scheme 7



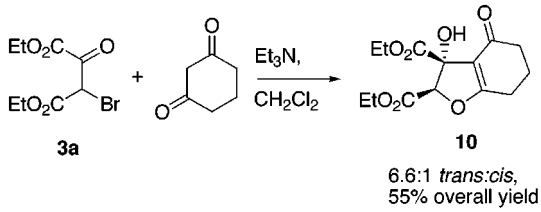
The turnover in selectivity for the dialdehyde reaction probably resulted from the relatively low pK_a of the nucleophile precursor. Making the nucleophile precursor more acidic had two consequences: the retro-aldol reaction became more favorable, and the cyclization became less favorable. The combination of these factors most likely led to cyclization rather than addition being the product-determining step for the dialdehyde reaction. Apparently, cyclization favored the *trans* isomer to a small degree. To reverse the selectivity, we resorted to use of the preformed sodium enolate under anhydrous conditions (Scheme 8).[11] These conditions resulted in a modest selectivity for the *cis*-isomer but were also accompanied by a moderate amount of bromine transfer and homocoupling to yield tetraester **1a**.

Scheme 8



Finally, we assayed cyclic β-diketones as the nucleophilic component in the reaction with bromooxaloacetates (Scheme 9). The condensation of 1,3-cyclohexadione with **3a** yielded dihydrofuran **10**. This particular β-diketone nucleophile yielded the *trans* dihydrofuran as the major product. The stereochemistry of the major product was confirmed by X-ray crystallographic analysis. The acidity of the diketone was not sufficient to explain the *trans* selectivity. The 3-oxopropionate likely had a similar pK_a yet yielded the *cis* product in high selectivity. As cyclohexadione was the sole cyclic enolate precursor tested, it is possible that *trans* selectivity

Scheme 9



(7) Sato, M.; Yoneda, N.; Katagari, N.; Watanabe, H.; Kaneko, C. *Synthesis* **1986**, 672−674.
(8) Shing, T. K. M.; Tai, V. W.-F.; Tam, E. K. W. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2312−2313.
(9) Hanessian, S.; Wong, D. H.-c.; Therien, M. *Synthesis* **1981**, 394−395.
(10) Bond, A. M.; Deprez, P. P.; Jones, R. D.; Wallace, G. G.; Briggs, M. H. *Anal. Chem.* **1980**, *52*, 2211−2213.
(11) Gómez-Sánchez, A.; Hermosín, I.; Lassaletta, J.-M.; Maya, I. *Tetrahedron* **1993**, *49*, 1237−1250.

resulted from the restriction of the intermediate enolate to the *E*-geometry.

In conclusion, we have proven that the "interrupted" Feist−Bénary reaction generally yields the *cis* isomer with moderately acidic nucleophiles and the *trans* isomer with more highly acid ones. We have proposed an explanation for this selectivity, based on addition or cyclization being the product-determining step. We have shown that a variety dicarbonyl compounds with appropriate acidities function as nucleophiles in this reaction. We are currently applying this reaction to the synthesis of the zaragozic acid core and developing an asymmetric version of the reaction.

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Supporting Information Available: Full experimental procedures and characterization data for **1a**, **2a**, **5**, **6**, **7a**,**b**, **8a**,**b**, **9** and **10** and representations of the X-ray crystal structures of **1a**, **6**, **9**, and **10**.

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