ORGANIC LETTERS

2005
Vol. 7, No. 21
4657−4660

Efficiency in Isotetronic Acid Synthesis via a Diamine−Acid Couple Catalyzed Ethyl Pyruvate Homoaldol Reaction

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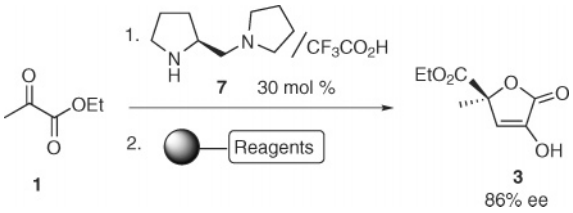
Received July 29, 2005

ABSTRACT



L-Proline failed to act as an organocatalyst in the homoaldol reaction of ethyl pyruvate; however, it reacted with the ester to give an azomethine ylide that in turn underwent 1,3-dipolar cycloaddition with a second molecule of pyruvate. Direct catalytic homoaldol reaction of ethyl pyruvate was performed using an (*S*)-(+)-1-(2-pyrrodinylmethyl)pyrrolidine/trifluoroacetic acid combination as organocatalyst. The use of polymer-supported reagents allowed for the lactonization of the aldol and isolation of the isotetronic acid derivative in hydroxy-free form.

In addition to the usual main reaction property, namely percent yield with respect to the intended target product, the paradigms of modern organic synthesis that may serve to evaluate the efficiency of a given transformation are based on various criteria including intrinsic (chemo-, regio-, and stereoselectivity, atom economy) and extrinsic (time, economy, environment) factors.[1] The burgeoning field of organocatalysis[2] is opening new opportunities to meeting the pressing need for low cost and environmentally friendly metal-free catalysts, while the development of new solution-phase techniques such as "light" fluorous,[3] tag-assisted,[4] and polymer-assisted solution-phase (PASP)[5] synthesis is aimed to simplify the crucial problem regarding the postreaction phases (workup and purification). We have set for ourselves a goal to consider both these issues in a single program dealing with the hitherto unexplored homoaldol reaction of ethyl pyruvate **1** under organocatalytic conditions and the elaboration of the resulting diethyl 2-hydroxy-2-methyl-4-oxoglutarate adduct **2** into the optically active isotetronic acid derivative **3** (Scheme 1) by using an orchestrated sequence of polymer-supported reagents and sequestrants (PASP approach). The homocoupling of **1** in an aldol-type reaction catalyzed by chiral bisoxazoline−metal(II) (Cu and Zn) complexes has been reported recently by Jørgensen and co-

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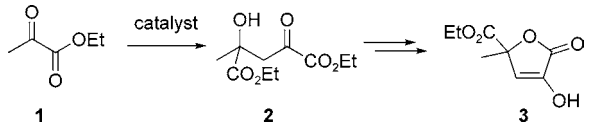
10.1021/ol051809p CCC: $30.25
Published on Web 09/17/2005

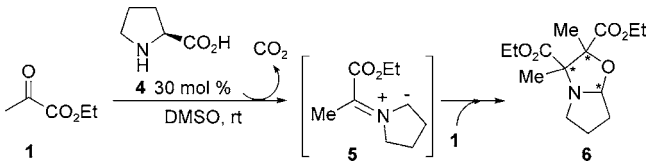
Scheme 1. Homoaldol Reaction of Ethyl Pyruvate



workers.[6] Quite surprisingly, to the best of our knowledge, the same homoaldolization reaction has not so far been considered via activation by a chiral organic catalyst mimicking the natural enzyme 4-hydroxy-2-oxo-4-methylglutarate aldolase (EC4.1.3.17).[7] A survey of the recent literature[8] indicates that most studies on organocatalysis have been mainly carried out using simple carbonyl compounds such as aldehydes and ketones. By contrast, systems of higher complexity such as α-ketoesters were only occasionally explored being the cross-aldol reaction of **1** with chloral the sole example reported.[8e] With the present work we intend to reduce this gap.

We began our study by considering the homoaldol reaction of ethyl pyruvate **1** in DMSO and promoted by L-proline **4**, the simplest and most common catalyst in the direct aldol reaction manifold (Scheme 2).[9] Unexpectedly, this reaction

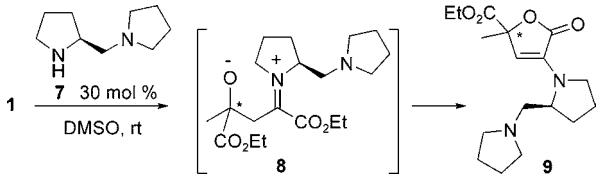
Scheme 2. Abortive Homoaldol Reaction of Ethyl Pyruvate under L-Proline Catalysis



instead of the aldol **2** afforded the 1-oxapyrrolizidine derivative **6** as a mixture of diastereoisomers in 95% overall yield. The formation of these compounds can be easily rationalized to occur through the azomethine ylide **5** arising from the addition of L-proline **4** to the ketoester **1** and decarboxylation. The 1,3-dipolar cycloaddition of the ylide **5** to the carbonyl of a second molecule of **1** would lead to **6**. Quite surprisingly, this side reaction of L-proline **4** has not been reported in earlier reactions exploiting this amino acid as a catalyst although this may be responsible of the low yields of aldols isolated in some cases.[10] However, the formation of 1-oxapyrrolizidines from the reaction of L-proline **4** with various nonenolizable aldehydes and occurring through a 1,3-dipolar cycloaddition process involving an azomethine ylide was reported in 1988 by Gariboldi and co-workers.[11,12]

As an alternative to L-proline **4**, the next stage of the research was centered on the use of (*S*)-(+)-1-(2-pyrrodinylmethyl)pyrrolidine **7**, a common tool in the arsenal of diamine organocatalysts.[13] Unlike that observed in the synthesis of aldols with quaternary carbon centers,[14] also this diamine was not prone to promoting the homoaldolization of ethyl pyruvate **1** in DMSO as the main product of the reaction was the adduct **9** incorporating one molecule of **7** (Scheme 3).[15] Evidently, compound **9** is formed via lactonization of the key intermediate **8**.

Scheme 3. Abortive Homoaldol Reaction of Ethyl Pyruvate under (*S*)-(+)-1-(2-Pyrrodinylmethyl)pyrrolidine Catalysis



Therefore, following the concept of Barbas[8f,9] and Yamamoto[13a−c] and their co-workers on the use of protic acid−diamine catalysts for direct asymmetric aldol reactions between suitable carbonyl systems, the homoaldolization of **1** was performed in DMSO using the diamine **7**/trifluoroacetic acid (TFA) couple in a catalytic amount (30 mol %). The analysis by ^{1}H NMR spectroscopy of the crude reaction mixture after 16 h excluded the formation of isotetronic acid **3** but revealed the complete conversion of ethyl pyruvate **1**

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(9) For a screening of amino acid catalysts in direct aldol reactions, see: Sakthivel, K.; Notz, W.; Bui, T.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2001**, *123*, 5260−5267.

(10) This possibility was already advanced by Barbas and co-workers, but experimental evidence on the cycloadduct formation was not provided. See: List, B.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2000**, *122*, 2395−2396.

(11) Orsini, F.; Pelizzoni, F.; Forte, M.; Destro, R.; Gariboldi, P. *Tetrahedron* **1988**, *44*, 519−541.

(12) The same result was observed by allowing ethyl pyruvate **1**, L-proline **4**, and *p*-nitrobenzaldehyde to react in DMSO wherein the Gariboldi-type products were exclusively observed.

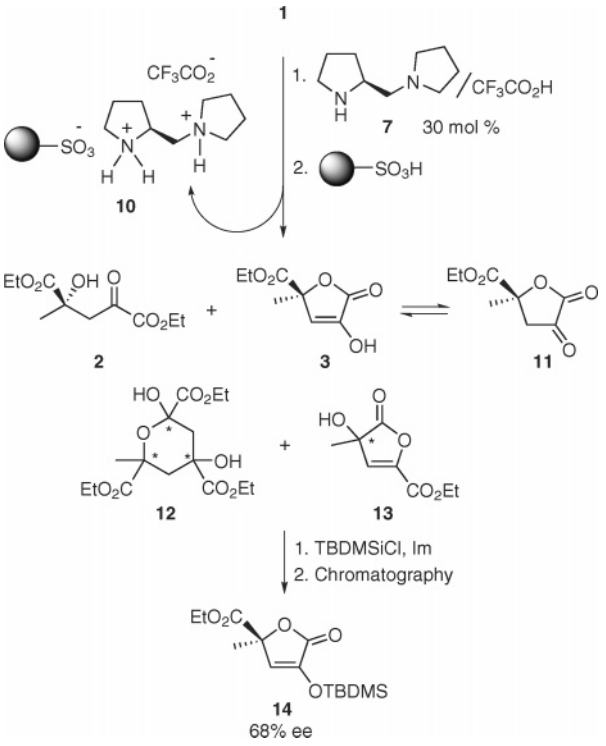
(13) (a) Saito, S.; Nakadai, M.; Yamamoto, H. *Synlett* **2001**, 1245−1248. (b) Nakadai, M.; Saito, S.; Yamamoto, H. *Tetrahedron* **2002**, *58*, 8167−8177. (c) Saito, S.; Yamamoto, H. *Acc. Chem. Res.* **2004**, *37*, 570−579. (d) Bolm, C.; Rantanen, T.; Schiffers, I.; Zani, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 1758−1763.

(14) Very good yield (93%) of the aldol although with poor enantiomeric excess has been reported. See ref 8f.

(15) The yields of **9** were 45% with respect to **1** and 74% with respect to **7**.

into a complex mixture of products whose isolation and purification by standard procedures, i.e., aqueous workup and chromatography, failed because of their lability under aqueous and acid conditions. Nevertheless, the ^{1}H NMR analysis of the reaction mixture was carried out with a good degree of accuracy after a suitable workup by means of the polymer-supported sulfonic acid Amberlyst 15, thus revealing the isotetronic acid **3** and its precursor homoaldol **2** as the major products of the conversion of **1** (Scheme 4 and entry

Scheme 4. Homoaldol Reaction of Ethyl Pyruvate under (*S*)-(+)-1-(2-Pyrrodinylmethyl)pyrrolidine/TFA Couple Catalysis

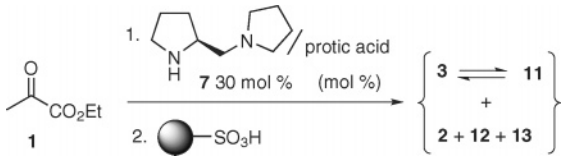


1 in Table 1). The acid resin[16] served to both sequester the catalyst as the bis-protonated diamine **10** and promote the formation of isotetronic acid **3** (in equilibrium with its dicarbonyl form **11**), and lactone **13**.[17] Notable in this reaction was the homoaldol catalytic trimerization of **1**, which as a side reaction afforded the cyclic product **12** in very low yield. To complete the analysis and evaluate the asymmetric induction of the reaction, the crude reaction mixture resulting from the treatment with Amberlyst 15 was treated with TBDMSiCl in CH_2Cl_2 under basic conditions (imidazole), thus inducing the conversion of **2**, **3**, and **11** into the *O*-silylated isotetronic acid derivative **14**. The enantiomeric excess (68%) in this compound was then evaluated by gas-chromatography using as chiral stationary phase Megadex 5. The absolute configuration of the stereocenter in **14** and

(16) Various scavenger resins were screened before Amberlyst 15 was identified as the most effective sequestering agent. Iminodiacetic acid, Cu(II)-functionalized iminodiacetic acid, 4-benzyloxybenzaldehyde, scavengerpore benzoic acid, and acetylpolystyrene resins proved to be ineffective.

(17) For a detailed scheme showing all the species involved, see Scheme S1 in the Supporting Information.

Table 1. Screening of Protic Acids and Solvents in the Homoaldol Reaction of **1** under **7**/Protic Acid Couple Catalysis[a]



entry	acid (mol %)	solvent	**2**[b]	**3** + **11**[b]	**12**[b]	**13**[b]	**14** (yield[c]) (ee[d])
1	TFA (30)	DMSO	23	71 + 4	1	1	53 (68)
2	TFA (30)	MeCN[e]	7	73 + 11	6	3	49 (57)
3	TFA (30)	DMF[e]	22	41 + 11	15	11	45 (60)
4	TFA (30)	*i*-PrOH	10	60 + 9	19	2	59 (86)
5	TFA (60)	*i*-PrOH	52	27 + 4	14	3	41 (84)
6	TfOH (30)	*i*-PrOH	7	11 + 65	17	0	51 (81)
7	TfOH (60)	*i*-PrOH[f]					
8	AcOH (30)	*i*-PrOH[g]	0	81 + 12	5	2	46 (34)
9	AcOH (60)	*i*-PrOH[g]	0	80 + 12	4	4	52 (53)
10	TFA (30)	*i*-PrOH[h]	7	50 + 5	35	3	41 (88)

[a] All reactions were run with 0.90 mmol of **1**, 0.27 mmol of **7**, and the reported amount of protic acid in the stated solvent at room temperature for 16 h. [b] Determined by ^{1}HNMR analysis of the crude reaction mixture (mol %). [c] Isolated yield (%). [d] Determined by chiral GC (%). [e] Reaction monitored after 60 h; conversion of **1** ~60%. [f] Conversion of **1** <5%. [g] Conversion of **1** ~80%. [h] Reaction run at −5 °C.

therefore in its precursors **2**, **3**, and **11** was assigned to be (*S*) by comparison of the optical rotation value with that reported for the same compound by Jørgensen and co-workers[6] (see the Supporting Information).

The efficiency of the diamine **7**−TFA combination was then screened using a series of different solvents, such as MeCN, DMF, and *i*-PrOH (Table 1). This study revealed *i*-PrOH to be the most effective solvent (entry 4) both in respect to the yield (59%) of isotetronic acid derivative **14** isolated and the degree of enantiomeric excess (86%). Screening the diamine **7**−acid combination in *i*-PrOH by using TFA and two more Brønsted acids, such as trifluoromethanesulfonic acid (TfOH) and acetic acid (AcOH) in different catalytic amounts, indicated that **7**/TFA in a 1:1 ratio was the best choice (entry 4). In the same way, also the variation of the temperature was evaluated showing that at −5 °C the ee (%) was slightly increased (entry 10) but the chemical yield was substantially diminished.

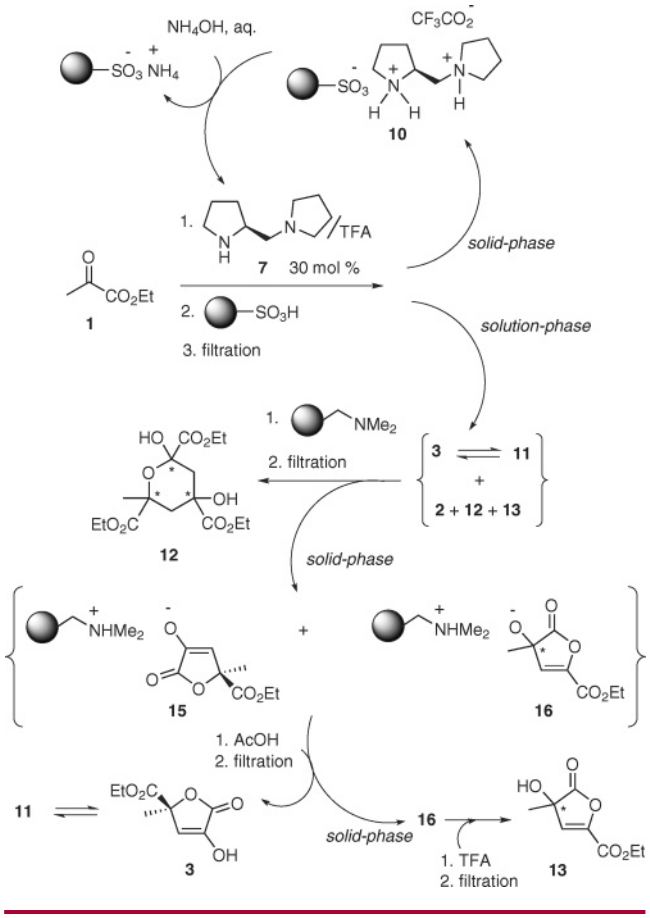
To date, there are four different synthetic approaches leading to isotetronic acids, namely: (a) the cobaloxamine-catalyzed photoinduced dimerization of alkyl pyruvates;[18] (b) the enantioselective aldol addition via hydrazones and lactonization;[19] (c) the asymmetric homoaldol reaction of pyruvates promoted by chiral Lewis acid complexes;[6] and (d) the basic racemic homodimerization of pyruvates.[20] To validate the utility of the homoaldolization of **1** under the

(18) Kijima, M.; Miyamori, K.; Sato, T. *J. Org. Chem.* **1988**, *53*, 1719−1722.

(19) Enders, D.; Dyker, H.; Leusink, F. R. *Chem. Eur. J.* **1998**, *4*, 311−320.

diamine **7**−TFA catalysis as an effective entry to isotetronic acid derivatives, we felt it essential to perform the isolation and purification of the target products in usable quantities and in their biologically active hydroxy-free form.[21] Our approach is based on the so-called polymer-assisted solution-phase (PASP)[5] synthesis that, unlike the solid-phase synthesis, consists of performing the reaction in solution followed by elaboration of the crude reaction mixture using polymer-supported reagents and sequestrants. This technique is especially aimed at recovering pure product(s) and catalyst by avoiding chromatographic separations and therefore is both labor and time saving and environmentally friendly. Thus, the crude reaction mixture (∼1 g) was first treated with Amberlyst 15, and the mixture filtered to give a solid constituted of the sequestered catalyst **10** (Scheme 5).

Scheme 5. PASP Synthesis of the Isotetronic Acid **3**



This material treated with aqueous ammonium hydroxide liberated the diamine **7**−TFA couple (70%) that remained in solution while the polymer-supported ammonium sulfonate was filtered off.[22] The solution containing the crude reaction mixture was treated with the basic resin Amberlyst 21 that induced the lactonization of the functionalized glutarate **2** to the isotetronic acid **3** and this was sequestered by the resin itself as the ammonium salt **15**. The same resin sequestered also the side product lactone **13** as the ammonium salt **16**. Filtration afforded a solution of the pure trimer **12** which was recovered in 12% yield. The solid material containing **15** and **16** was then treated first with AcOH that released exclusively the lactone **3** due to the weaker basic character of the conjugate base of **15** with respect to **16**. After filtration, the solution furnished pure isotetronic acid derivative **3** in 55% (230 mg) yield and in the hydroxy free form as required for biological studies. The remaining solid material was treated with the stronger acid TFA to liberate the lactone **13** in less than 5% yield.

In conclusion, we evidenced the inability of L-proline to serve as an organocatalyst in the homoaldol reaction of ethyl pyruvate **1** because of the decarboxylative process of an iminium intermediate that leads to an azomethine ylide. The bifunctional amine-acid catalyst approach by the use of the (*S*)-(+)-1-(2-pyrrodinylmethyl)pyrrolidine **7**−TFA combination solved the problem as it provided a highly enantioselective access to diethyl 2-hydroxy-2-methyl-4-oxoglutarate **2**, the homoaldol of **1**. Consequently, a two-step biomimetic and new synthesis of isotetronic acid **3** has been reported. The new scheme relies on the use of supported reagents and scavenger resins that allow for a chromatography-free isolation and purification of all products as well as the recovery of the catalyst.

Acknowledgment. We gratefully acknowledge MIUR (COFIN 2004) for financial support.

Supporting Information Available: Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL051809P

(20) Braña, M. F.; García, M. L.; López, B.; de Pascual-Teresa, B.; Ramos, A.; Pozuelo, J. M.; Domínguez, M. T. *Org. Biomol. Chem.* **2004**, *2*, 1864−1871.

(21) For biological properties and synthetic utility of isotetronic acids, see ref 19.

(22) The use of the recycled catalyst **7**−TFA in the homoaldol reaction of **1** under optimized conditions (entry 4, Table 1) afforded identical results in term of both product distribution and ee%.