(Scheme II) was confirmed through CAD analysis of the peak at m/z 379, which afforded p-toluenesulfonate ion (m/z 171) as the only negatively charged product.

In an effort to further elaborate on the nature of the substitution reaction occurring in the ditosylates, methyl 2,6-dideoxy-3-*O*-(*p*-tolylsulfonyl)-α-D-*arabino*-hexopyranoside (**5**) and methyl 2,6-dideoxy-3-*O*-(*p*-tolylsulfonyl)-4-*O*-(methylsulfonyl)-α-D-*arabino*-hexopyranoside (**6**) were analyzed. The monotosylate **5** led to the expected spectrum consisting of a very small parent peak at m/z 316 and a base peak at m/z 225 corresponding to the sulfite ion. No peak corresponding to formation of the p-toluenesulfonate ion was observed in the negative-ion MS of **5**. Thus it is the presence of a second sulfonate group, as in the case of the ditosylate **2**, that permits internal substitution.

The combined mesylate tosylate **6** produced peaks at m/z 394 (parent radical anion, relative abundance ≤1%), m/z 379 (M – CH_3 from the methylsulfonyl group, vide infra, 10% relative abundance), m/z 303 (M – tosyl, 100% relative abundance), m/z 171 (p-toluenesulfonate ion, 10% relative abundance), and m/z 95 (methanesulfonate ion, 5% relative abundance). From these data it can be seen that the initially formed radical anion cleaves to give either of two sulfite anions **7** or **8** (Scheme III). Internal nucleophilic displacement in **7** produces the p-toluenesulfonate ion while internal nucleophilic substitution in **8** produces the methanesulfonate ion. In order to prove these suppositions, CAD analysis was performed on both ions **7** and **8**. Ion **7** produced p-toluenesulfonate ion exclusively, and ion **8** produced methanesulfonate ion exclusively.

From these data it can be seen that formation of a p-toluenesulfonate ester radical anion in the gas phase leads to exclusive homolytic cleavage of the S–C bond as depicted in Scheme II.[14] In marked contrast to this is the solution-phase chemistry, where initial photochemical generation of the radical anion via an electron-transfer process in alcoholic solutions leads to cleavage of the p-toluenesulfonate esters at the S–O bond as outlined in Scheme I. To our knowledge this is the first example of a complete alteration in the course of a unimolecular fragmentation due solely to a solvent effect. The most reasonable explanation for this phenomenon is the difference in basicity of the alkoxide ion in the gas phase and in hydroxylic solvents. The extreme base strength (and resulting high energy of the corresponding ion) observed for an alkoxide ion in the gas phase[15] makes cleavage to form this ion directly a difficult process. In solution where this ion is well stabilized by its solvent cage, cleavage in this manner requires much less energy and therefore is more feasible.

Acknowledgment. We thank the Standard Oil Co. for support of this research and the Lewis Research Center (NASA) for donation of the Finnigan TSQ-45 mass spectrometer used in this work.

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(14) Bowie has examined the negative-ion mass spectrum of ethyl benzenesulfonate and observed ions resulting from cleavage between both the C–S and the S–O bond; however, this work was performed under high energy electron impact conditions, which are expected to produce much more extensive fragmentations. Nolde, C.; Madsen, J. O.; Lawesson, S.-O.; Bowie, J. H. *Ark. Kemi* **1969**, *31*, 481.

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A Selective Method for the Direct Conversion of Aldehydes into β-Keto Esters with Ethyl Diazoacetate Catalyzed by Tin(II) Chloride

Christopher R. Holmquist and Eric J. Roskamp*

Department of Chemistry, Northwestern University, Evanston, Illinois 60208-3113

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Summary: Aldehydes are efficiently converted into β-keto esters by the addition of ethyl diazoacetate in the presence of tin(II) chloride.

Sir: β-Keto esters have been prepared by a variety of methods.[1] We have found that aldehydes can be converted into β-keto esters directly by the addition of ethyl diazoacetate in the presence of a catalytic amount of tin(II) chloride. Several early papers report this transformation under thermal conditions;[2] however, these conditions do not appear to be general as exemplified by the reaction of *n*-heptanal which leads to a dioxolane.[3] To the best of our knowledge there is no convenient method for the *direct conversion* of aldehydes into β-keto esters.[4] The analogous reaction for ketones has been described and extensively studied.[5]

Initially our aim was to generate an alkylidene-type reagent by reacting ethyl diazoacetate with a low-valent

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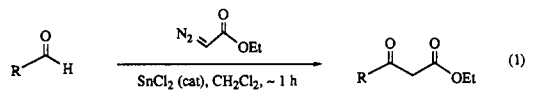
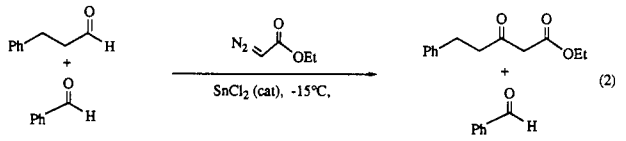
main group metal. This reagent could then convert an aldehyde into an alkene via a pseudo-Wittig type reaction.[6] When we attempted this reaction to our surprise no olefinic products were observed; however, the reaction did produce a single product, a β-keto ester (eq 1). Our examination of this reaction is described herein.



(1)

This reaction is catalyzed by a variety of Lewis acids (e.g., BF_3, $ZnCl_2$, $ZnBr_2$, $AlCl_3$, $SnCl_2$, $GeCl_2$, $SnCl_4$). The best results were obtained with BF_3, $GeCl_2$, and $SnCl_2$. For the reaction of hydrocinnamaldehyde with ethyl diazoacetate the following yields were obtained, BF_3 (67%), $GeCl_2$ (73%), $SnCl_2$ (86%) with 10 mol % catalyst. For primary aldehydes less than 5 mol % catalyst can be used for tertiary and aromatic aldehydes require additional catalyst[7] (see Experimental Section). Common solvents (e.g., THF, Et_2O, DME, CH_3CN, CH_2Cl_2, $PhCH_3$) can be used. However, in ether, THF, DME, and CH_3CN the rates were considerably slower and/or there were additional side products. Ultimately, we chose methylene chloride because it gave the best results and was easiest to remove. The reaction also appears to be relatively insensitive to the atmosphere. Identical reactions run under nitrogen, in open flasks, with water added or $SnCl_2$–$2(H_2O)$ as catalyst, all yielded comparable results.

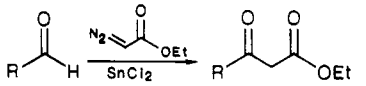
The two most noteworthy aspects of this reaction are its selectivity and the mild conditions. As we examined a range of substrates we observed that the yields and relative rates of reation were lower with aromatic substances (Table I). This suggested that a differentiation of two types of aldehydes might be possible. A reaction performed on a 1:1:1 mixture of benzaldehyde, hydrocinnamaldehyde, and ethyl diazoacetate gave a 14:1 ratio of β-keto esters at room temperature and a 30:1 ratio at −15 °C (eq 2). The mild conditions of this reaction are illustrated with the reaction of phenylacetaldehyde, which does not readily enolize under these conditions (Table I). Citronellal, which undergoes a facile intramolecular cyclization in the presence of acid,[8] under these conditions yields 80% β-keto ester and 5% isopulegol. Nitro groups (entry 6) were not reduced at an appreciable rate to effect the outcome of the reaction.[9]

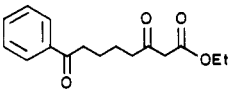
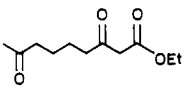
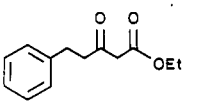
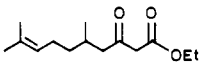
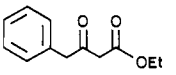
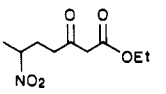
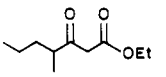
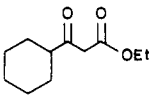
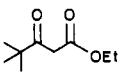
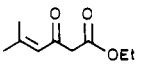
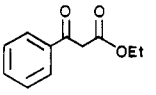
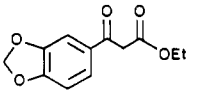


(2)

The following representative procedure was used;[10] methylene chloride (8 mL) followed by ethyl diazoacetate (0.45 g, 3.9 mmol) was added with stirring at room temperature to anhydrous tin(II) chloride[11] (0.07 g, 0.37 mmol).

Table I



β-keto ester[a]	yield,[b] %
 1	90
 2	75
 3	86
 4	80
 5	71
 6	80
 7	81
 8	80
 9	65
 10	60
 11	50
 12	35

[a] The β-keto esters were characterized by ^1H and ^{13}C NMR, IR, MS, C, H, N analysis for all new compounds and/or comparison with authentic material. [b] All yields are of isolated product.

To this suspension were added a few drops of hydrocinnamaldehyde (0.5 g, 3.7 mmol) in methylene chloride (2 mL). When nitrogen evolution began the remaining

(6) Riviere, P.; Castel, A.; Satge, J. *J. Am. Chem. Soc.* **1980**, *102*, 5415.
(7) It appears that in the slower the reactions (i.e. aromatics) the catalyst is consumed by the enol form of the β-keto ester at a rate which is competitive with keto ester formation. This produces a metalated enol which no longer catalyses the reaction.
(8) Clark, B., Jr.; Chamblee, T.; Iacobucci, G. *J. Org. Chem.* **1984**, *49*, 4557.
(9) Bellamy, F.; Ou, K. *Tetrahedron Lett.* **1984**, *25*, 839.
(10) All reactions were performed under an inert nitrogen atmosphere. Methylene chloride was distilled from CaH_2. Ethyl diazoacetate and anhydrous tin(II) chloride were obtained from Aldrich and used without any further purification. The aldehydes were distilled prior to being used. The TLC plates were developed with an alcoholic solution of $FeCl_3$ (20 g/200 mL of isopropyl alcohol).
(11) The tin(II) chloride does not initially dissolve. With primary and secondary aldehydes the reaction becomes homogeneous near its completion.

solution of cinnamaldehyde was added dropwise over 10 min. After nitrogen evolution had stopped[12] (~1 h) the reaction was transferred to a separatory funnel with saturated brine (NaCl, 40 mL)[13] and extracted with diethyl ether (2×, 80 mL).[14] The organic layers were combined and dried ($MgSO_4$) and the volatiles removed under vacuo. The remaining oil was either chromatographed on silica gel 60 (hexane/ethyl acetate) or the smaller keto esters could be distilled (the higher molecular weight ones tend to undergo a fair amount of decomposition).

(12) Aromatic and tertiary aldehydes reacted much slower with only a very moderate rate of nitrogen evolution. When initial nitrogen evolution had stopped with these substrates the reactions were somewhat cloudy and still had a greenish color, characteristic of the diazoacetate. We added an additional amount of tin(II) chloride to these reactions and observed additional nitrogen evolution. This procedure was repeated until there was no longer any nitrogen evolution observed.

(13) To this was added 1% KOH, which helped in reducing or eliminating the emulsion formed from the tin chloride. This was not used in every case to avoid any base-catalyzed reactions.

(14) Alternatively the methylene chloride can be removed in vacuo and the crude product chromatographed directly.

Articles

Total Synthesis of 3(*S*)-Carboxy-4(*S*)-hydroxy-2,3,4,5-tetrahydropyridazine, an Unusual Amino Acid Constituent of Luzopeptin A†

Philip Hughes*,‡ and Jon Clardy

Baker Laboratory of Chemistry, Cornell University, Ithaca, New York 14853

Received January 31, 1989

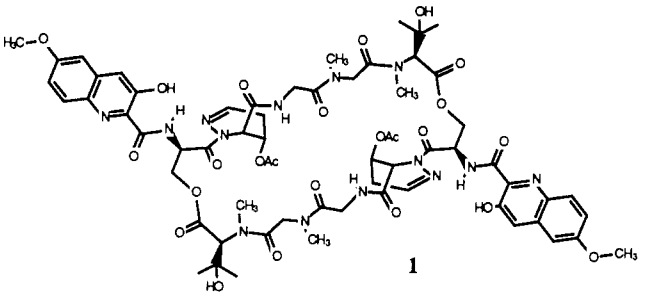
The enantiospecific synthesis of 3(*S*)-carboxy-4(*S*)-hydroxy-2,3,4,5-tetrahydropyridazine (2), a novel constituent of the antibiotic antitumor agent luzopeptin A is described. Structural corroboration of the synthetic compound is based on three points. The ^{13}C NMR spectrum of synthetic **2** was compared with that of a similar degradation product of luzopeptin. The ^{1}H NMR spectrum of **2** was compared with that of the synthetic cis isomer. Finally, the synthetic methodology developed for the synthesis of **2** was applied to the synthesis of the known L-*trans*-3-hydroxyproline.

Introduction

An increasingly popular approach to the development of therapeutic agents involves the design of compounds that closely mimic natural peptide hormones or substrates. Generally, this entails reducing the natural peptide to a minimally required size and replacing normal amino acids and peptide regions with synthetic analogues that confer desired properties such as enhanced binding, hydrolytic stability, or antagonism verses agonism. New nonstandard amino acids, which might serve to replace normal amino acids, are often discovered in natural products. Such compounds also offer, besides their possible therapeutic utility, challenging synthetic targets.

A soil screening program at the Bristol-Banyu Research Institute in Tokyo, aimed at finding new compounds with promising antitumor activity, recently led to the isolation of a series of antitumor antibiotics from *Actinomadura luzonesis*. Chemical degradation studies by Konishi and co-workers[1] and single-crystal X-ray diffraction studies by Arnold and Clardy[2] defined the structure of the major and most active compound as **1**, originally named BBM-928A but since renamed luzopeptin A.

Luzopeptin, a dimeric cyclic depsipeptide, is a bis-intercalator of DNA and this is thought to play a role in its activity.[3] The six unique constituents of luzopeptin are four known amino acids, a new quinoline, and an interesting new "amino acid": 2(*S*)-carboxy-3(*S*)-hydroxy-2,3,4,5-tetrahydropyridazine (**2**). This ring system was previously unknown in nature though it has since been found in the cirratiomycin antibiotics.[4] The hexahydropyridazine carboxylic acids are known, occurring in the monamycin antibiotics.[5] The synthesis of luzopeptin analogues where the pyridazine has been replaced with a simpler amino acid has also been reported.[6] We report here an enantioselective synthesis of this new amino acid.



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† Taken from the thesis of P. Hughes, Cornell University, 1983.

‡ Present address: Wyeth-Ayerst Research, Box CN 8000, Princeton, NJ 08543-8000.

(1) Konishi, M.; Ohkuma, H.; Sakai, F.; Tsuno, T.; Koshiyama, H.; Naito, T.; Kawaguchi, H. *J. Am. Chem. Soc.* **1981**, *103*, 1241-1243.
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(3) Arnold, E. Thesis, 1982, Cornell University.
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