Tetrahedron Letters,Vol.31,No.3,pp 315-318,1990 0040-4039/90 $3.00 + .00
Printed in Great Britain Pergamon Press plc

CONJUGATE ADDITION OF LITHIUM DIORGANOCUPRATE REAGENTS TO THE ENOL TOSYLATE OF A 1,2-DIKETONE

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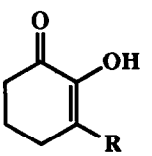
Summary: The conjugate addition of lithium diorganocuprate reagents to the enol tosylate of 1,2-cyclohexanedione has been investigated. The intermediate enolates eliminate *para*-toluenesulfinate ion to generate the alkylated 1,2-dicarbonyl system.

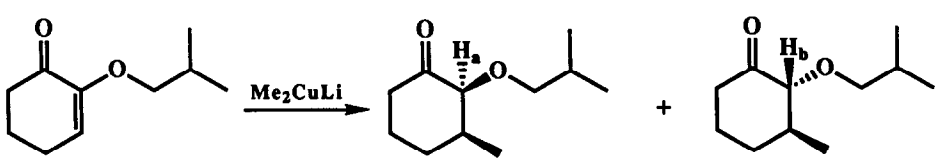
The alkylated 1,2-dicarbonyl system **1** is an important subunit in a number of antileukemic agents, e.g. bruceantin.[1,2] Interestingly, various flavoring agents found in coffee are simple alkylated 1,2-dicarbonyl



1

compounds as well.[3] We were interested in exploring the synthesis of these diketones via the conjugate addition of lithium diorganocuprate reagents to derivatives of the corresponding unsubstituted 1,2-dicarbonyl unit.[4,5]

At the outset of this work, only one example was found of a cuprate addition to an enol derivative of a 1,2-diketone. In that communication, Hanessian reported the addition of lithium dimethylcuprate to the enol benzoate of a sugar-derived 1,2-diketone.[6] We considered it valuable to determine if derivatives other than enol benzoates were acceptable. Thus, treatment of the isobutyl enol ether **2** with lithium dimethylcuprate in diethyl

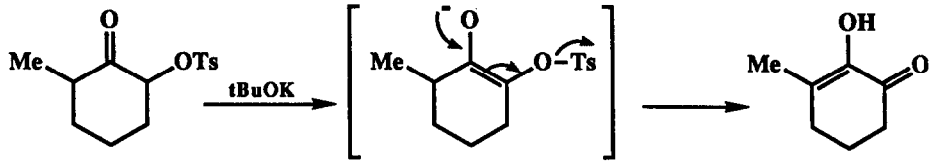


2 **3** **4**

ether at 0 °C followed by a methanol quench gave the ketones **3** and **4** in 92% yield as a 60:40 mixture. The products were separated by flash chromatography[7] and identified spectroscopically. The ^{1}H NMR of **3** showed

H_a as a doublet of doublets at δ3.52 (J = 1, 4 Hz), whereas the ^1H NMR spectrum of **4** showed H_b as a doublet at δ3.41(J = 10 Hz). Further evidence for the above assignments came from separate equilibrations of pure **3** and **4** with sodium methoxide in methanol. Each sample led to a 27:73 mixture of **3**:**4** as judged by capillary vapor phase chromatography.

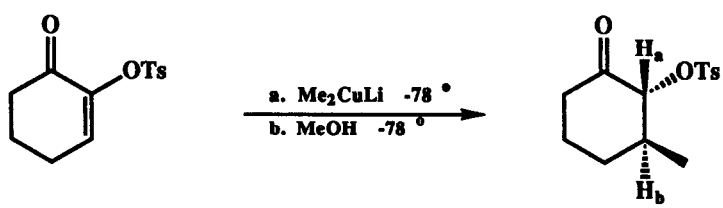
Next, the corresponding enol tosylate **5** was studied to determine if it was a viable substrate for cuprate additions. This interest was based on an unpublished report by Levine that the α-tosyloxyketone **6** was converted into the enolized 1,2-diketone **7** via a novel base-induced elimination of *para*-toluenesulfinate ion.[8]



6 **7**

None of the expected Favorskii product was observed. We were interested in the generation of an enolate analogous to Levine's intermediate via the conjugate addition of a lithium diorganocuprate reagent to an enol tosylate.

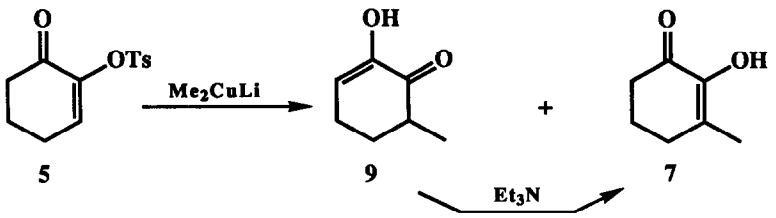
The enol tosylate **5**[9] was exposed to lithium dimethylcuprate in diethyl ether at -78 °C for three hours, followed by a methanol quench at that temperature. After chromatographic separation, 67% of the α-tosyloxy-



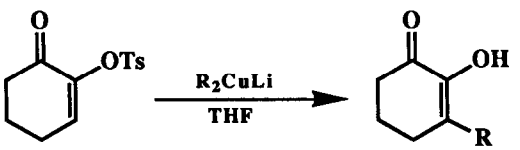
5 **8**

ketone **8**[10] and 10% of recovered **5** was obtained. None of the corresponding *cis* stereoisomer was observed.

It was found that *in situ* elimination of *para*-toluenesulfinate ion was effected when the reaction mixture from the addition of lithium dimethylcuprate to the enol tosylate **5** was warmed to room temperature prior to the protic quench. The resultant product, a ca. 1:1 mixture of **7** and **9**, was converted into the more stable isomer **7** by treatment with triethylamine in dichloromethane. As expected, conjugate addition of lithium dimethylcuprate to the enol tosylate **5** was found to be slower in tetrahydrofuran than in diethyl ether.[11] However, tetrahydrofuran was the solvent of choice due to the enhanced rate of elimination of *para*-toluenesulfinate ion in that medium.



All lithium diorganocuprate reagents studied to date have afforded good yields of the corresponding diketones **1**. Continuing work is focused on establishing the scope, limitation and application of this very interesting reaction.



R	YIELD
Me	83%
Et	80%
nBu	75%
secBu	63%
Ph	75%

Representative experimental procedure:

Lithium dimethylcuprate was prepared in freshly distilled (sodium/benzophenone ketyl) tetrahydrofuran (THF) at 0 °C (20 mL, 0.02 M, 0.4 mmol).[11] The reaction mixture was cooled to -78 °C and the enol tosylate **5** (100 mg, 0.4 mmol) was added as a THF solution (3 mL total). The reaction mixture was warmed to room temperature and stirred for 135 minutes at that temperature. Then pH 8 NH_4Cl/NH_4OH was added and the reaction mixture was diluted with 50 mL of diethyl ether. The organic phase was extracted three times with NH_4Cl/NH_4OH solution. Then the organic phase was dried ($MgSO_4$), filtered and evaporated *in vacuo* to yield 41 mg of an oil. This oil was dissolved in 5 mL of 5:1 dichloromethane/triethylamine and stirred at room temperature for four hours. Evaporation *in vacuo* followed by flash chromatography afforded 39 mg of the diketone **7** (83% yield) as a crystalline solid, identical spectroscopically with an authentic sample.[3,5]

Acknowledgements:

We are very grateful to Professor Gilbert Stork for his interest and helpful discussions. This work was supported by a grant from the Surdna Foundation.

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5. See Kende, A. S.; Eilerman, R. G. *Tetrahedron Lett.* **1973**, 697-700 for an alternative method to synthesize this system, based upon the alkylation of the bis(enolate) of a 1,2-diketone.

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10. The α-tosyloxyketone **8** was shown to be a single compound by thin layer chromatography, melting point (110-111 °C), ^{1}H NMR [H_a: δ4.70 (d, J_{ab} = 11 Hz)] and elemental analysis.

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(Received in USA 3 November 1989)