$SnCl_4$ Mediated Rearrangement of α-Aroyl-γ-butyrolactone: Reinvestigation of the Mechanism

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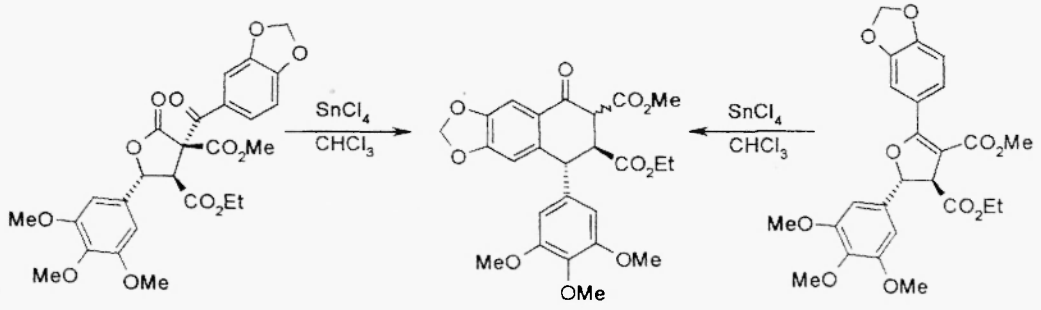
Abstract: The mechanism of $SnCl_4$-mediated rearrangement of α-aroyl-γ-butyrolactones into aryl tetralones was reinvestigated and was compared to the rearrangement of 2,5-diaryl-2,3-dihydrofurans using the same conditions. We have shown that in fact lactone is converted into dihydrofuran which then is rearranged into a tetralone.

Introduction

4-aryltetralones are highly valuable synthons used as key intermediates for the synthesis of biologically active compounds such as Sertraline (Zoloft®) (1), ABT-431 (2-3) and many other active molecules (4-8). Two efficient syntheses of 4-aryltetralones such as **1**, based on a $SnCl_4$-induced rearrangement of oxygenated heterocycles like 2,5-diaryl-2,3-dihydrofuran **2** (9) or α-aroyl-γ-butyrolactone **3** (10) have been reported in literature (Scheme 1).



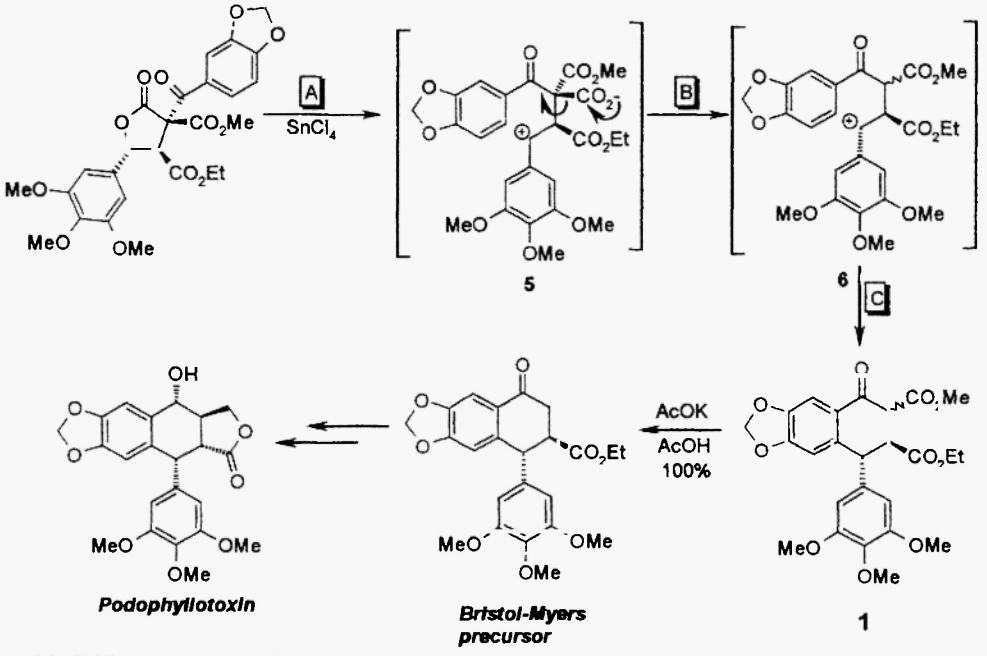
3 1 2

SCHEME 1. synthesis of 4-aryltetralones

Results and discussion

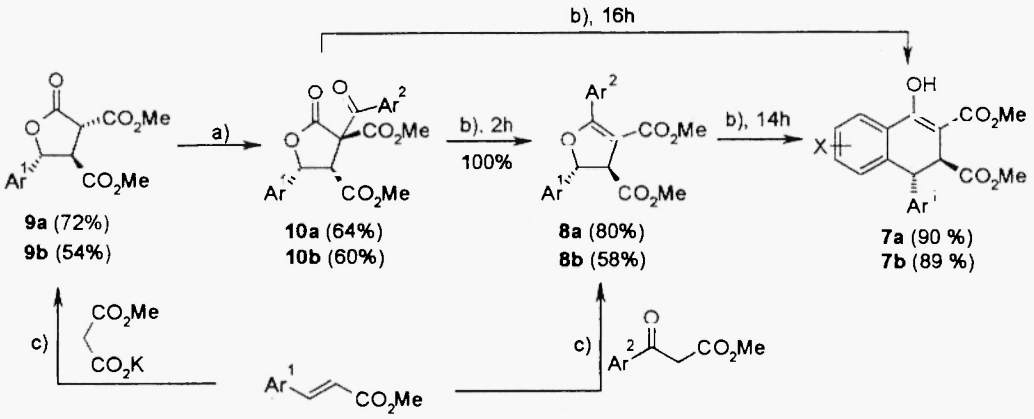
$SnCl_4$-induced rearrangement of the α-aroyl-γ-butyrolactone **3** is an efficient method to obtain the 4-aryltetralone **1** as the key step for the synthesis of the Bristol-Myers precursor of the well known anticancer agent podophyllotoxin,. After 24h, this reaction cleanly led to **1** in 91% yield. According to the authors, the

rearrangement is a stepwise mechanism and proceeds as described in Scheme 2. In a first step initial opening of the lactone gives the benzylic carbocation **5** (step A); decarboxylation of **5** gives the carbocation **6** (step B) which undergoes intramolecular Friedel and Craft reaction leading to **1**. Based on our expertise in the field of that type of rearrangement (11), we suspected that the proposed mechanism is different from the first one proposed. Thus we decided to reinvestigate this type of rearrangement and to compare the route with that starting from the 2,5 –diaryl-2,3-dihydrofuran **2**.



SCHEME 2. Synthesis of Podophyllotoxin

Formation of the two tetralones **7a** and **7b** already used as precursors of natural products (10,12) was thus studied (Scheme 3). The starting heterocyclic species could efficiently be obtained by $Mn(OAc)_3$ mediated addition of dicarbonylated compounds (β-ketoester for the 2,3-dihydrofurans **8a** and **8b**, monomethylmalonate for γ-lactones **9a** and **9b**) to methyl cinnamate moieties in acetic acid at 70°C. Formation of 2,5-diaryl-2,3-dihydrofurans **8** gave roughly better yields than synthesis of the γ-lactones **9**. In all cases reaction was totally regio- and diastereoselective leading to the single *trans*-**8** and *trans,trans*-**9** diastereomers. Subsequently, tetralone precursors **10** were prepared by α-aroylation of the sodium enolates of **9** in THF.

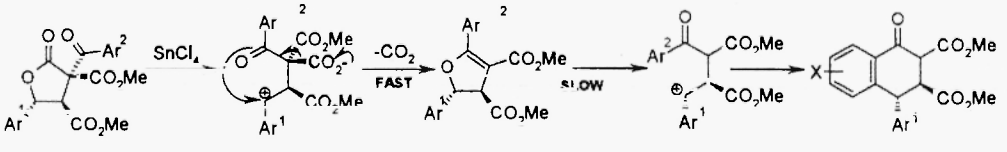


a=Ar¹=Ar²= 3,4-dimethoxyphenyl
b=Ar¹= 3,4-triméthoxyphenyl; Ar²= 3,4-methylenedioxyphenyl

a) 1) NaH, THF, r.t.; 2) aroyl chloride, r.t., 6h. b) $SnCl_4$, CH_2Cl_2, r.t. c) $Mn(OAc)_3$, AcOH, 70°C.

SCHEME 3. Preparation of the substrates

As described, the $SnCl_4$-induced rearrangement of **8** or **10** in CH_2Cl_2 at room temperature led to 4-aryltetralones **7** in nearly 90% yield. However, when rearrangement of **10** was checked at regular intervals by TLC the total consumption of **10** and formation of intermediary product was detected after 2h; this intermediate was then slowly converted into **7**. This new product was isolated and unambiguously characterized as being **8**. In opposition to the commonly accepted mechanism, the rearrangement of the α-aroyl-γ-butyrolactones is a two step reaction beginning by conversion of the γ-lactone to a 2,3-dihydrofuran which consecutively rearranges into 4-aryltetralone. It means that the unique heterocyclic compounds leading to 4-aryltetralones by Lewis-acid rearrangement are the 2,5-diaryl-2,3-dihydrofurans. The crucial step of this mechanism is decarboxylation of acyclic benzylic carbocation resulting from the γ-lactone ring opening. This carbocation is trapped by enol form of the β-ketoester resulting from carbon dioxide loss (scheme 4) leading to the 2,5-diaryl-2,3-dihydrofuran. This transformation is a fast and quantitative process. A slower transformation takes then place involving the 2,3-dihydrofuran ring opening followed by intramolecular Friedel et Crafts cyclization.



SCHEME 4. Mechanism of the rearrangement leading to a tetralone

Conclusion

In summary, we have demonstrated that in the $SnCl_4$-induced rearrangement of γ-lactones route for the synthesis of 4-aryltetralones the true intermediates are 2,5-diaryl-2,3-dihydrofurans which can be used directly as precursors. Furthermore this rearrangement can be used for the synthesis of 2,5-diaryl-2,3-dihydrofurans provided that reaction time is controlled.

Experimental part

General procedure for the preparation of 2,3-dihydrofurans 8: α-aroyl-γ-butyrolactones (0.04 M solution in CH_2Cl_2) are stirred under nitrogen at room temperature. 10 equiv. of $SnCl_4$ are added in one portion via a syringe and stirring is continued until total consumption of starting material (2h). The reaction mixture is then diluted with Et_2O followed by careful addition of satured aqueous $NaHCO_3$. The aqueous layer are extracted with Et_2O. The combined organic layers are washed with satured aqueous $NaHCO_3$ and dried over $MgSO_4$. After evaporation of the solvent, the crude product is purified by flash chromatography (hexane/Et_2O) to give **8a** in 80% yield and **8b** in 58% yield.

8a: ^{1}H-NMR ($CDCl_3$): 3.60 (s, 3H), 3.72 (s, 3H), 3.81 (s, 6H), 3.86 (s, 6H), 4.17 (d, 1H, *J*= 6.6), 5.61 (d, 1H, *J*= 6.6), 6.75-6.82 (m, 4H), 7.56 (dd, 1H, *J*= 1.3, 8.6), 7.62 (d, 1H, *J*= 1.6). ^{13}C-NMR ($CDCl_3$): 51.35, 52.68, 56.11, 56.16, 58.39, 84.87, 100.60, 108.86, 110.33, 111.52, 113.10, 118.16, 121.53, 123.52, 132.65, 138.11, 148.23, 149.55, 151.62, 164.95, 166.64, 173.45.
8b: ^{1}H-NMR ($CDCl_3$): 3.61 (s, 3H), 3.75 (s, 3H), 3.78 (s, 3H), 3.80 (s, 6H), 4.16 (d, 1H, *J*= 6.5), 5.58 (d, 1H, *J*= 6.5), 5.95 (s, 2H), 6.52 (s, 2H), 6.88 (d, 1H, *J*= 7.8), 7.42 (d, 1H, *J*=1.3), 7.50 (dd, 1H, *J*=1.3, 7.8). ^{13}C-NMR ($CDCl_3$): 51.44, 52.79, 56.30 ($2CH_3$), 58.14, 60.96, 85.10, 100.81, 101.67, 102.43 (2CH), 107.90, 110.02, 122.53, 124.99, 135.59, 138.20, 147.28, 150.12, 153.74 (2C), 164.78, 166.18, 173.30.

References

(1) M. Lautens and T. Rovis *J. Org. Chem.* **1997**, *62*, 5246.

(2) S. A. Castner, G. V. Williams and P. S. Goldman-Rakie *Science* **2000**, *287*, 2020.

(3) O. Rascol, O. Blin, C. Thalamas, S. Descombes, C. Soubrouillard, P. Azulay, N. Fabre, F.Viallet, K. Lafnitzegger, S. Wright, J. Carter and J. Nutt *Ann. Neurol.* **1999**, *45*, 736.

(4) D. M. Vyas, P. M. Skonezny, T. A. Jenks and T. W. Doyle *Tetrahedron Lett.* **1986**, *27*, 3099.

(5) K. Negash, D. E. Nichols, V. J. Watts and R. B. Mailmman *J. Med. Chem.* **1997**, 40, 2140.

(6) W. Quaglia, M. Pigini, A. Piergentili, M. Giannella, F. Gentili, G. Marucci, A. Carrieri, A. Carotti, E. Poggesi, A. Leonardi and C. Melchiorre *J. Med. Chem.* **2002**, *45*, 1633.

(7) G. J. Quallich and T. M. Woodall *Tetrahedron* **1992**, *47*, 10239.

(8) E. J. Corey and T. G. Gant *Tetrahedron Lett.* **1994**, *35*, 5373.

(9) F. Z. Yang, M. K. Trost and W. E. Fristad *Tetrahedron Lett.* **1987**, *28*, 1493.

(10) J. R.Peterson, H. D. Do and R. D. Rogers *Synthesis* **1991**, 275.

(11) F. Garzino, A. Méou and P. Brun *Tetrahedron Lett.* **2002**, *43*, 5049.

(12) F. Garzino, PhD thesis, Universite de la Méditerranée, France, 2001.

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