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anti Ethyl β-thienyl-β-amino-α-hydroxy propionate: a regio and stereoselective ring opening of *trans* ethyl 2-thienyl-glycidate

A. Solladié-Cavallo,[a,*] P. Lupattelli,[a,b,*] C. Bonini[b] and M. De Bonis[a,b]

[a]*Laboratoire de stéréochimie organométallique associé au CNRS, ECPM/Université L. Pasteur, 25 rue Becquerel, 67087 Strasbourg, France*

[b]*Dipartimento di Chimica, Università degli Studi della Basilicata, Via Nazario Sauro 85, 85100 Potenza, Italy*

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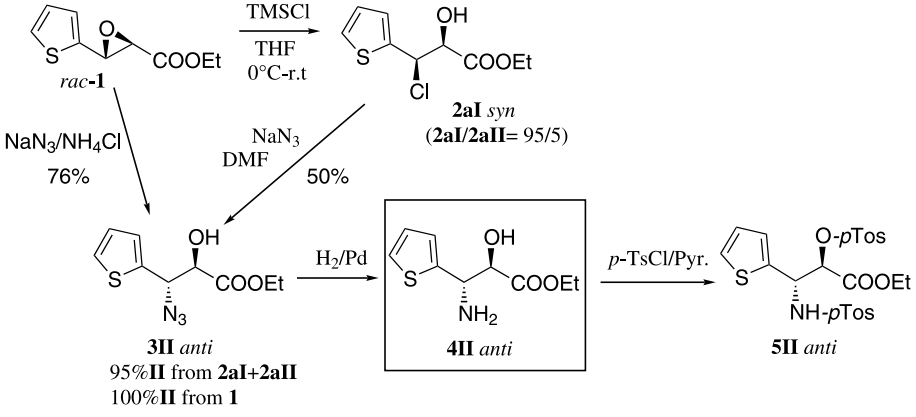
Abstract—*anti* Ethyl β-thienyl-β-amino-α-hydroxy propionate was obtained regio- and diastereo-selectively in three steps and 45% overall yield, while 95% *syn* ethyl β-chloro-β-thienyl-α-hydroxy ester was obtained regio-selectively in two steps and 50% overall yield, both from 2-thienyl aldehyde.

The synthesis of aromatic α-hydroxy-β-aminoacids is a current matter of research, because these compounds constitute a substructure of several naturally occurring biologically important substances. The thienyl ring represents an interesting moiety, because it efficiently mimics the phenyl ring in certain pharmacologically active compounds, some of which for instance are used as surgical anaesthetics in both humans and veterinary practices.[1] Substitution of phenyl by a five-membered aromatic heterocycle in the Taxol amino hydroxy side chain has recently produced compounds with remarkable antitumor and antileukemia properties.[2]Although one of the most successful ways to synthesise α-hydroxy-β-aminoacids is the ring opening of glycidic esters by a nitrogen nucleophile, its application to *trans* β-thienyl glycidic esters gave β-amino derivatives in low yield (and as *syn*/*anti* mixtures)[3] or as the minor product of mixtures where the α-amino derivative is major.

We present here two ways to obtain erythro β-amino-α-hydroxy esters as the major and unique aminohydroxy derivative from *trans* β-thienyl glycidic ethyl ester **1** (Scheme 1).

The *trans* thienyl glycidate **1** was prepared via a Darzens reaction[3] between 2-thienyl aldehyde and ethyl chloroacetate. It is worth noting that the Knoevenagel



Scheme 1.

Keywords: β-thienyl esters; α-hydroxy-β-amino esters; heteroaromatic epoxides.

* Corresponding authors. Tel.: +33 3 90 24 27 72; fax: +33 3 90 24 27 06; e-mail: cavallo@chimie.u-strasbg.fr

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side product **6**[4] is always present in small amount (10–15%) whatever the base used (Scheme 2). However, avoiding the NH_4Cl work-up procedure by a direct filtration and evaporation of the solvent, it has been possible to prevent formation of other side products (due to opening of **1**) and to obtain the desired epoxide in 85–90% yield.

Separation of epoxide **1** from compound **6** can be performed by chromatography over silicagel treated with 1% NEt_3 ($\sim$60% isolated yield).

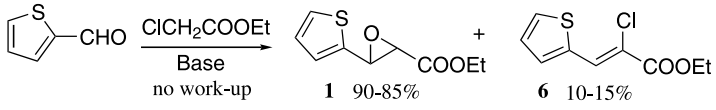
Various halogen-providing reagents have been used for the opening of epoxide **1** (Scheme 3), and the results are gathered in Table 1.

Among the four possible isomers (**2I**, **2II**, **7I** and **7II**) only two were observed and they have been identified as the two diastereomers **I**-*syn* and **II**-*anti* of regioisomer **2** (cf. below). And, most interestingly, regioisomer **7** has not been observed under the conditions used.

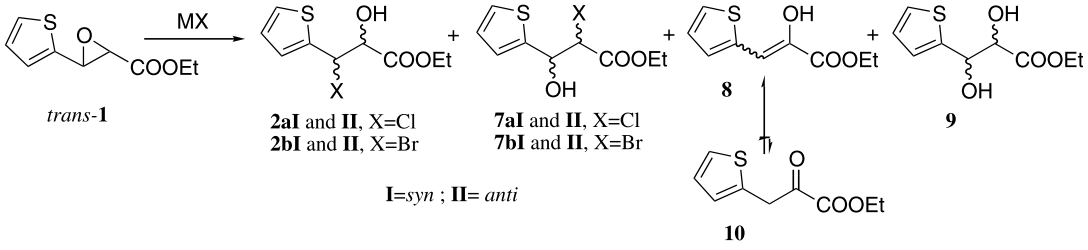
The enol **8**[5] of ketone **10** (coming from rearrangement of the epoxide) (Scheme 3) is always present and is often the major product. The rearrangement is catalysed by Amberlyst-H^+ (Table 1, lines 4, 5), by H^+ from HX (Table 1, lines 6, 7) formed during treatment of the crude product (addition of H_2O and NH_4Cl), by H^+ from HX (Table 1, line 9) present in the reagent or by the metal (Table 1, line 2). Moreover, partial conversion of the halohydrin into enol **8** could be considered, as pure isolated chlorohydrin **2a** slowly converted to a 1/1 mixture of **2a** and **8** after 3 days at 0–5°C (detected by ^1H NMR).

Diol **9**[6] was mainly observed (19 and 28%) when Amberlyst 15 were used (Table 1, lines 4 and 5) and is due to humidity present in the Amberlyst. In the case where $MgBr_2$–Et_2O was used, the traces of diol **9** come from the treatment with H_2O used to eliminate the salt.

It appeared that opening of *trans*-**1** either with $MgCl_2$ in Et_2O at room temperature or with TMSCl in THF (without work-up) are the only interesting reactions conditions able to provide 68 and 86% of the desired regioisomer **2** of the chlorohydrin in which the *syn* is major (Table 1, lines 6 and 8). However, opening with



Scheme 2.

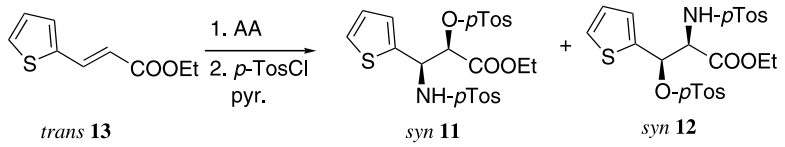


Scheme 3.

Table 1. Opening of epoxide **1** with halogen-providing reagents

Reagent	React. cond.	Work-up	Products[a]		
			2I+**2II**[b] (**2I**/**2II**)	**8**	**9**
LiCl (3 equiv.)	Acetone, −78°C	No[c]	No reaction		
LiBr (3 equiv.)	Acetone, −78°C	No[c]	0	100	0
NaBr (3 equiv.)	Acetone, −30°C	No[c]	No reaction		
LiCl (3 equiv.)/Amberlyst 15	Acetone, −78°C	No[c]	28	43	28
NaBr (3 equiv.)/Amberlyst 15	Acetone, −30°C	No[c]	24	57	19
$MgCl_2$ (4 equiv.)	Et_2O, rt	NH_4Cl	**68** (**71**/29)	**18**	**0**
$MgBr_2$:OEt_2 (4 equiv.)	Et_2O, −78°C	H_2O	13	84	3
TMSCl (1.8 equiv.)	THF, rt	No[c]	**86** (**95**/5)[e]	**14**	**0**
TMSBr (1.8 equiv.)[d]	THF, rt	No[c]	45 (95/5)	55	0

[a] Ratios were determined by ^1H NMR on the crude products of the reactions.
[b] Regioisomer **7** was not observed.
[c] After filtration the solvent was evaporated under vacuum.
[d] Not distilled (contains traces of HBr).
[e] Compound **2aI** *syn* is largely major (Scheme 1).



Scheme 4.

TMSCl in THF, which provides the highest yield (86%) and 95% of the desired *syn* isomer, is the only one useful.

It is reasonable to postulate that the 29% of *anti*-**2II** obtained by using $MgCl_2$ are mainly due to activation by $MgCl_2$ and *trans* opening at C3 by $MgCl_2$ complexed to the carbonyl as already suggested in the literature[3,7] because, when the reagent is a covalent compound (TMSCl), only 5% of this isomer is detected.

Opening of *trans* thienyl epoxide **1** with $TMSN_3$ has already been shown[3] to provide mainly the *anti* stereoisomer (92%) of regioisomer **7** (opening at C2), the *syn* stereoisomer of regioisomer **2** (opening at C3) being the minor product (8%). All the opening studied here occurred at C3 and TMSCl provided the *syn* isomer as the major one. It can thus be concluded that openings by TMS(Z) reagents at C2 and C3 undergo through different mechanisms, as already suggested by Plumet.[3]

The desired *anti* β-amino-α-hydroxy ester **4II** was then obtained in two steps (45% overall yield) through **2aI** (three steps) (Scheme 1).

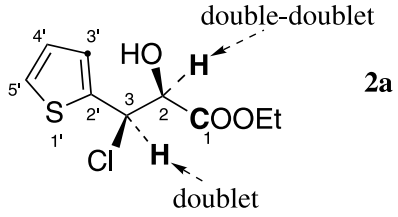
However, and most interestingly, the use of NaN_3/NH_4Cl at reflux and in a THF/dioxane/H_2O mixture (1/10/10)[2] provided directly the desired regioisomer of the *anti* azide **3II** (Scheme 1), in high yield and complete diastereoselectivity (only one diastereomer detected: **3II**) which provides a two-step and about 70% yield synthesis of **4II**.

Characterisation of chlorohydrin 2aI

The signal ($\delta = 4.48$ ppm) of one of the methine proton being a double-doublet ($^3J_{23} = 2$ Hz, $^3J_{2OH} = 8$ Hz) was assigned to CHOH because of the presence of a coupling constant with the OH proton. Assignment of the second methine proton CHCl (doublet at 5.65 ppm, $^3J_{32} = 2$ Hz) was then straightforward.[8]

The thienyl ring C3′ carbon was assigned using COSY and NOESY experiment. The **2aI** structure (with Cl at C3) was assigned using long-range $^1H/^{13}C$ correlation. A correlation spot is indeed observed between the thienyl ring C3′ carbon and the CHCl proton (doublet).

The *syn* configuration of **2aI** was then assigned indirectly, by converting **2aI** into **5II** (Scheme 1) which was then compared with the *syn* compounds **11** and **12** obtained by *cis*-aminohydroxylation[9] of *trans* olefin **13** (Scheme 4). Both compounds **11** and **12** are unambiguously *syn* and exhibit ^1H and ^{13}C NMR spectra different from those of compound **5II**. It can thus be concluded that **5II** is *anti* and, as a consequence, that **2aI** is *syn* (Scheme 1).



2a

In conclusion, *anti* β-amino-β-thienyl-α-hydroxy esters can be obtained in three steps and 45% overall yield from 2-thienyl aldehyde, while *anti* α,β-dihydroxy-β-thienyl esters (or any desired β-substituted α-hydroxy-β-thienyl esters) can be prepared from *syn* β-chloro-β-thienyl-α-hydroxy esters available regio- and diastereoselectively in two steps from 2-thienyl aldehyde.

Acknowledgements

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4. **6**: ^1H NMR (200 MHz, $CDCl_3$): δ: 8.13 (s, 1H, H3), 7.60 (d, $^3J = 4$ Hz, 1H, H7), 7.52 (d, $^3J = 3.5$ Hz, 1H, H5), 7.15 (dd, $^3J = 4$ Hz, 3.5 Hz, 1H, H6), 4.35 (q, $^3J = 8$ Hz, 2H, CH_2), 1.39 (t, $^3J = 8$ Hz, 3H, CH_3). The assignments have been made by direct and long range $^1H/^{13}C$ correlation.
5. **8**: ^1H NMR (400 MHz, $CDCl_3$): δ: 7.45 (d, $^3J = 6$ Hz, 1H, H5′), 7.31 (d, $^3J = 4$ Hz, 1H, H3′), 7.08 (dd, $^3J = 6$ Hz, 4 Hz, 1H, H4′), 6.82 (s, 1H, H3), 6.50 (brs, 1H, OH), 4.40 (q, $^3J = 7$ Hz, 2H, CH_2), 1.40 (t, $^3J = 7$ Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$):δ: 165.9 (C1), 137.9, 137.4 (C2,

C2′), 129.3, 128.5, 127.5 (C3′, C4′, C5′), 106.1 (C3), 62.8 (CH_2), 14.6 (CH_3). The assignments have been made by direct and long range $^1H/^{13}C$ correlation.

6. **9**: ^1H NMR (200 MHz, $CDCl_3$) thienyl and ester signals identical to those of **2a** and two doublets: 5.27 (d, $^3J=2$ Hz, H3), 4.44 (d, $^3J=2$ Hz, H2).
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8. **2aI**: ^1H NMR (400 MHz, $CDCl_3$): δ: 7.35 (d, $^3J=5$ Hz, 1H, H5′), 7.23 (d, $^3J=3.5$ Hz, 1H, H3′), 6.98 (dd, $^3J=5$ Hz, $^3J=3.5$ Hz, 1H, H4′), 5.65 (d, $^3J=2$ Hz, 1H, H3), 4.48 (dd, $^3J_{23}=2$ Hz, $^3J_{2OH}=8$ Hz, 1H, H2), 4.35 (q, $^3J=6$ Hz, 2H, $C\underline{H}_2CH_3$), 1.4 (t, $^3J=6$ Hz, 3H, $CH_2\underline{CH}_3$). ^{13}C NMR (100 MHz, $CDCl_3$); δ: 171.1 (C1), 140.8 (C2′), 131.6, 131.89, 129.9 (C4′, C3′, C5′), 62.9 ($\underline{C}H_2CH_3$), 59.8 (C3), 74.8 (C2), 14.5 ($CH_2\underline{C}H_3$).
2aII: δ: 4.68 ($^3J_{23}=4$ Hz, $^3J_{2OH}=8$ Hz, 1H, H2), 5.59 ($^3J_{23}=4$ Hz, 1H, H3).
The assignments have been made by direct and long range $^1H/^{13}C$ correlation.
9. Schlingloff, G.; Sharpless, K. B. In *Asymmetric Oxidation Reactions, A Practical Approach in Chemistry*; Katsuki, T., Ed.; Oxford University Press: New York, 2001; p. 104.