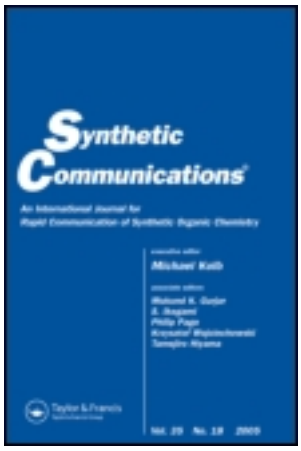

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SYNTHESIS OF α-AMINOORTHOESTERS FROM *O*-TOSYLHYDROXIMATES

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ABSTRACT

The abstraction of the acid hydrogen of *O*-tosylhydroximates **1** by sodium ethylate, then nucleophilic attack of the excess of sodium ethylate at the more hindred carbond atom of azirine **2** and aziridine **3** intermediates to give the α-aminoorthoesters (35–45% yields). The α-aminoorthoester **4a** is transformed into α-iminoorthoesters **5a** (63% yield) and α-amidoorthoester **6a** (65% yield).

Key Words: α-Amidoorthoesters; α-Aminoorthoesters; Aziridines; Azirinines; α-Iminoorthoesters; Nucleophilic ring opening; O-tosylhydroximates

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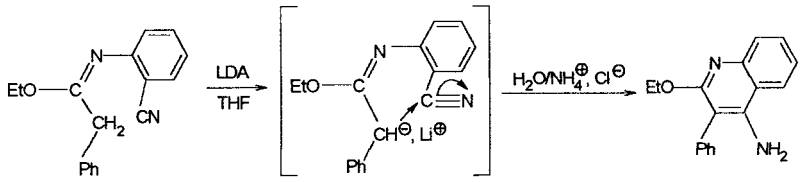
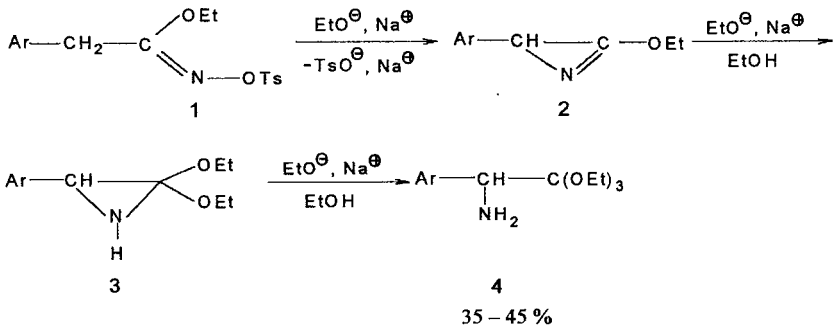


Scheme 1.

We have previously reported that the imidate derivatives gave oxazolines,[1] oxazoles,[2] benzoxazines,[3] quinoleines[4] and triazoles[5] by reaction with organometallic compounds and hydrazines. We have also shown that *N*-2-cyanophenylethylbenzimidate was transformed into aminoquinoline by the action of LDA being the base abstracting the acid hydrogen and completing the reaction (Scheme 1).[6]

We have studied in this paper the effect of the replacement of the cyanophenyl group by well-leaving groups, and we used another base such as the sodium ethylate. So, the reaction of *O*-tosylhydroximates **1a–d** with an excess of sodium ethylate in ethanol at room temperature for six days gave the α-aminoorthoesters **4a–d** with 35–45% overall yields (Scheme 2).



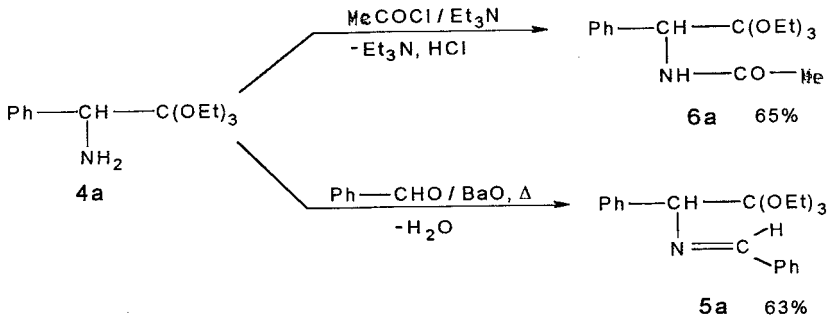
a: Ar = Ph ; **b**: Ar = p-Me-Ph ; **c**: Ar = p-Cl-Ph, **d**: Ar = Th

Scheme 2.

To explain the unexpected product **4**, we may suggest that in the first step of the reaction, the ethylate anion abstracted the acid hydrogen of the methylene group of *O*-tosylhydroximate **1** to give an intermediate, which cyclised into azirine **2**. The same nucleophile attacked the latter instable azirine **2** at the more hindred carbon atom, then attacked the aziridine **3** and yielded the α-aminoorthoester **4** (Scheme 2).

However, when we treated the *O*-acetyl, *O*-trimethylsilyl and *O*-oxodiethoxyphosphorylhydroximates by sodium ethylate we regenerated the starting hydroximates, these three latter products were derived by the specific nucleophilic attack at the more electrophile center. The abstraction of the hydrogen atom of *O*-tosyloximes followed by cyclization into azirines then ring opening of the corresponding aziridines into α-aminoketones by an excess of sodium ethylate also have been reported by Neber.[7]

Moreover, Graham[8] has shown that the reaction of *N*-chloroiminoesters with sodium ethylate yielded α-aminoorthoesters. The acid hydrolysis of the latter products gave α-aminoesters, the water molecule attacked the orthoester group. In the present investigation, we have treated the compound **4a** with benzaldehyde and acetylchloride. The products **5a** (63%) and **6a** (65%) were formed by nucleophilic attack of the amine group of **4a** at the carbonyl group of these two precedent reagents (Scheme 3).



Scheme 3.

From these results, we can conclude that the synthesis of α-aminoorthoesters appears to depend on the degree of leaving group activation.

EXPERIMENTAL

General: Melting points were determined with Büchi apparatus and are uncorrected. IR spectra were run on a Perkin Elmer IR-681 infrared spectrometer in $CHCl_3$ solution. ^1H NMR spectra were recorded on a Jeol EM (60 MHz) in $CDCl_3$ solution. Chemical shifts are expressed in ppm with reference to TMS as an internal standard coupling constants given in Hz. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet.

Synthesis of α-aminoorthoesters 4 from *O*-tosylhydroximates 1: To a stirred solution of 1 (1 mol) in dry ether (50 ml) was added a solution of sodium in absolute ethanol (100 ml) at 0°C, and the reaction mixture was stirred at room temperature for 6 days. The sodium tosylate was filtered and the solvent was evaporated under normal pressure. The residue was distilled under reduced pressure to yield (35–45%) of **4**.

Orthoester 4a: $B.p._{0.5} = 35°C$. Yield, 45%. IR: 3390, 3315, 1630 (NH_2), 1605 (C=C), 1285, 1120 (C–O). ^1H NMR: 1.10 (t, $J = 5$, 9H), 1.74 (s, 2H), 3.55 (q, $J = 5$, 6H), 4.06 (s, 1H), 6.80–7.90 (m, 5H).

Orthoester 4b: $B.p._{0.5} = 90°C$. Yield, 40%. IR: 3390, 3310, 1660 (NH_2), 1610 (C=C), 1280, 1110 (C–O). ^1H NMR: 1.25 (t, $J = 5$, 9H), 2.10 (s, 2H), 2.83 (s, 3H), 3.56 (q, $J = 5$, 6H), 4.53 (s, 1H), 7.00–8.00 (m, 4H).

Orthoester 4c: $B.p._{0.3} = 110°C$. Yield, 40%. IR (KBr): 3380, 3310, 1660 (NH_2), 1635 (C=C), 1280, 1120 (C–O). ^1H NMR: 1.16 (t, $J = 5$, 9H), 1.73 (s, 2H), 3.60 (q, $J = 5$, 6H), 4.10 (s, 1H), 7.30 (m, 4H).

Orthoester 4d: $B.p._{0.1} = 124°C$. Yield, 35%. IR: 3420, 3360, 1660 (NH_2), 1640 (C=C), 1280, 1120 (C–O). ^1H NMR: 1.20 (t, $J = 5$, 9H), 2.10 (s, 2H), 3.60 (q, $J = 5$, 6H), 4.35 (s, 1H), 7.17–7.34 (m, 3H).

Reaction of 4a with benzaldehyde: A mixture of **4a** (5.1 g, 0.02 mol), benzaldehyde (2.12 g, 0.02 mol), BaO (2.75 g, 0.02 mol) and dry xylen (20 ml) was refluxed for 18 h. The precipate of BaO, H_2O was filtered and the xylen was evaporated. The crude product was distilled to give the yellow liquid of **5a.**

Orthoester 5a: $B.p._{18} = 120°C$. Yield, 63%. IR: 1670 (C=N), 1660 (C=C), 1280, 1120 (C–O). ^1H NMR: 1.10 (t, $J = 5$, 9H), 3.50 (q, $J = 5$, 6H), 4.10 (s, 1H), 4.45 (s, 1H), 7.20 (m, 10H).

Reaction of 4a with acetyl chloride: To a solution of **4a** (5.10 g, 0.02 mol) in Et_3N (3 g, 0.03 mol) was added a solution of acetyl chloride (1.57 g, 0.02 mol) in dry ether (30 ml) at 0°C. The reaction mixture was stirred at ambient temperature for 24 h, and then the precipate of Et_3N, HCl was filtered. The excess of Et_3N and ether was removed in vacuo to afford the product as white crystal of **6a**.

Orthoester 6a: M.p.: 70°C. Yield, 65%. IR: 3440 (N–H), 1665 (C=O), 1600 (C=C), 1280, 1120 (C–O). ^1H NMR: 1.10 (t, $J = 5$, 9H), 1.19 (s, 3H), 3.50 (q, $J = 5$, 6H), 5.20 (s, 1H), 6.40 (s, 1H), 7.20 (m, 5H).

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