Pergamon

Tetrahedron Letters, Vol. 37, No. 30, pp. 5417-5420, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01060-X

PALLADIUM CATALYSED REARRANGEMENT OF ALLYLIC SULFOXIMINES: SYNTHESIS OF γ-AMINO α,β-UNSATURATED KETONES AND ESTERS

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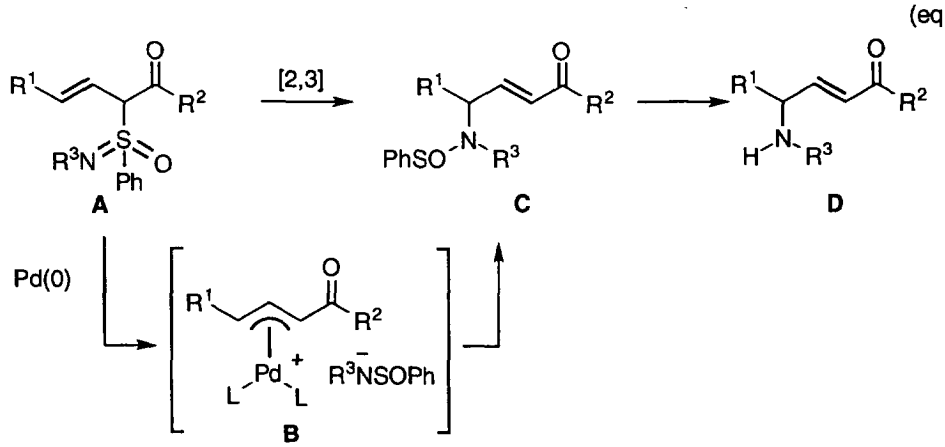
Abstract: The synthesis of γ-amino α,β-unsaturated ketones and esters from the palladium(0) catalysed rearrangement of (*E*) α–sulfonimidoyl β,γ-unsaturated ketones and esters is reported.

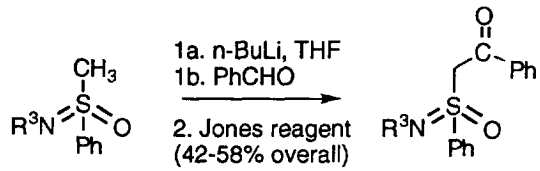
γ-Amino α,β-unsaturated ketones and esters are useful substrates for natural product and bioactive molecule synthesis.[1,2] The latter amino compounds have often been found as important structural elements of peptide-like protease inhibitors.[3] γ-Amino α,β-unsaturated esters are readily prepared from the Wittig-Horner reaction of *N*-protected α-amino aldehydes that are available in a few synthetic steps from naturally occurring α-amino acids.[2,4] This methodology however, is clearly only convenient for the preparation of γ-amino α,β-unsaturated esters from naturally occurring α-amino acids.[5] As part of a synthetic project we required a general method for the preparation of γ-amino α,β-unsaturated ketones and esters that could not be prepared from "the pool" of naturally occurring α-amino acids. Based on our previous success on the synthesis of chiral allylic amines from the palladium(0) catalysed rearrangement of allylic sulfoximines to allylic sulfinamides[6-8] we reasoned that the analogous palladium(0) catalysed rearrangement of α–sulfonimidoyl β,γ-unsaturated ketones **A** (R^2 = alkyl, aryl) and esters **A** (R^2 = OR) to the allylic sulfinamides **C** would give a route to the desired γ-amino α,β-unsaturated ketones and esters **D** (eq 1). While in principle the thermal [2,3] sigmatropic rearrangement of **A** would give **C** such thermal rearrangements are often inefficient or non-regioselective.[8-10]

(eq 1)



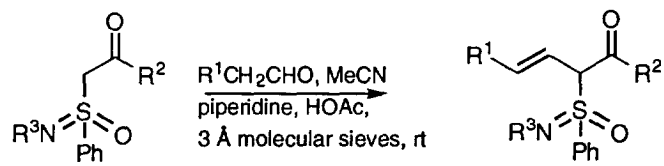
The α–sulfonimidoyl β,γ-unsaturated ketones **3a,b** and ester **3c** were prepared by a Knoevenagel type condensation of the α-sulfonimidoyl ketones **2a** or **2b** or the known α-sulfonimidoyl ester **2c**[11] with aldehydes as shown in equation 3. The α-sulfonimidoyl ketones **2a** and **2b** were conveniently prepared according to equation 2 via an aldol like condensation of the carbanions derived from the *S*-methyl sulfoximines **1a**[12] and **1b**[11] with benzaldehyde followed by Jones oxidation of the resulting diastereomeric mixture of carbinol compounds. The Knoevenagel type condensation reactions proceeded in modest to good yields (46-87 %) and gave the desired (*E*) α–sulfonimidoyl β,γ-unsaturated ketones **3a** and **3b** and the (*E*) α–sulfonimidoyl β,γ-unsaturated ester **3c** as mixtures of two diastereomeric compounds (Table 1).

(eq 2)



1a; R^2 = Ph, R^3 = Ts **2a; R^3 = Ts**
1b; R^2 = Ph, R^3 = CO_2Me **2b; R^3 = CO_2Me**

(eq 3)



2a; R^2 = Ph, R^3 = Ts **3a; R^2 = Ph, R^3 = Ts**
2b; R^2 = Ph, R^3 = CO_2Me **3b; R^2 = Ph, R^3 = CO_2Me**
2c; R^2 = OMe, R^3 = Ts **3c; R^2 = OMe, R^3 = Ts**

Table 1. Synthesis of **3a-c**

aldehyde (R^1)	product	reaction time (h)[a]	yield(%)[b]	d. r.[c]
n-Bu	**3a**; R^1 = n-Bu	4.5	47	74 : 26
n-Bu	**3b**; R^1 = n-Bu	24	46	76 : 24
n-pent	**3a**; R^1 = n-pent	6	53	76 : 24
n-pent	**3b**; R^1 = n-pent	24	65	69 : 31
n-hexyl	**3a**; R^1 = n-hexyl	5	53	88 : 12
Et	**3c**; R^1 = Et	5	87	58 : 42

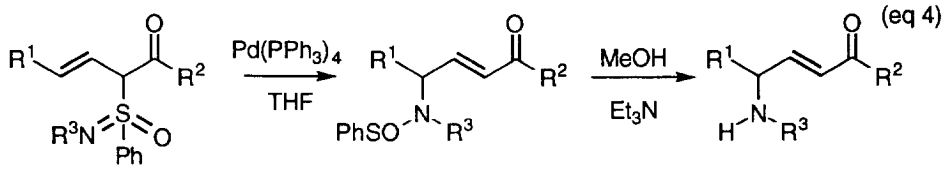
[a] Not optimised . [b]After purification by column chromatography. [c]Determined by ^{1}H NMR

Treatment of the individual (*E*) α–sulfonimidoyl β,γ-unsaturated ketones **3a** or **3b** or the ester **3c** with 10 mol % of freshly prepared tetrakis(triphenylphosphine)palladium(0) ($(PPh_3)_4Pd$) in dry THF solution at room temperature gave a red or orange coloured solution. TLC analysis of the reaction mixtures after 1h indicated complete consumption of the starting allylic sulfoximines. ^{1}H NMR analysis of the crude reaction mixtures showed the formation of the often unstable allylic sulfinamides **4a-c.** In the case of the *N*-Ts allylic

sulfinamides **4a** and **4c** (R^3 = Ts) these appeared as single diastereomeric products while in the case of **4b** (R^3 = CO_2Me) mixtures (75-85 : 25-15) of diastereomeric products were evident. Mild methanolysis of the reaction mixtures with triethylamine / methanol at rt gave pure (*E*)-sulfonamides **5a,c** and the (*E*)-carbamate **5b** after purification of the crude reaction mixtures by column chromatography (silica gel) in overall yields of 32-68 % as shown in Table 2.

We have briefly examined the thermal rearrangement of **3a** and **3b** in acetonitrile at 70-75°C. While the former substrates do undergo rearrangement to **4a** the latter compounds give a complex mixture of products.

The extension of this methodology to the asymmetric synthesis of γ-amino α,β-unsaturated ketones and esters and the application of these substrates to the asymmetric synthesis of bioactive molecules is currently under active investigation.



3a; R^2 = Ph, R^3 = Ts **4a; R^2 = Ph, R^3 = Ts** **5a; R^2 = Ph, R^3 = Ts**
3b; R^2 = Ph, R^3 = CO_2Me **4b; R^2 = Ph, R^3 = CO_2Me** **5b; R^2 = Ph, R^3 = CO_2Me**
3c; R^2 = OMe, R^3 = Ts **4c; R^2 = OMe, R^3 = Ts** **5c; R^2 = OMe, R^3 = Ts**

Table 2. Synthesis of **5a-c** from **3a-c**.

starting compound	product	yield(%)[a]	mp (°C)
3a; R^1 = n-Bu	**5a**; R^1 = n-Bu	32	103-104
3b; R^1 = n-Bu	**5b**; R^1 = n-Bu	64	oil
3a; R^1 = n-pent	**5a**; R^1 = n-pent	60	99
3b; R^1 = n-pent	**5b**; R^1 = n-pent	49	oil
3a; R^1 = n-hexyl	**5a**; R^1 = n-hexyl	68	ND
3c; R^1 = Et	**5c**; R^1 = Et	57	oil

[a] After purification by column chromatography.

Experimental

The synthesis of the α–sulfonimidoyl β,γ-unsaturated ketone **3b** (R = n-Bu),*a general procedure*: To a stirred mixture of the sulfoximine **1b** (0.269 g, 0.85 mmol), hexanal (0.2 mL, 1.66 mmol) and 3 Å molecular sieves (ca 1 g) in acetonitrile was added a solution of piperidine (18 μL, 0.18 mmol) and acetic acid (21 μL, 0.36 mmol) in acetonitrile (3 mL). The mixture was stirred at rt for 24h under an atmosphere of nitrogen. The cloudy yellow solution was then filtered and the solvent was removed *in vacuo*. Purification of the crude product on a short column of silica gel using initially 5% ethyl acetate / hexane and finally 10% ethyl acetate / hexane as eluent gave the title compound as a yellow oil (155 mg, 46 %) and as a 76 : 24 mixture of diastereoisomers. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.2-7.2 (m, 10H), 7.07 (d, *J* = 9.3 Hz, H1, major diast.),

6.41 (d, J = 9.3 Hz, H1, minor diast.), 6.1-5.9 (m, 1H), 5.3-5.4 (m, 1H), 3.80 (s, OMe, major diast.), 3.51 (s, OMe, minor diast.), 2.1-0.7 (m, 9H).

The synthesis of the (E)-carbamate **5b** (R = n-Bu), *a general procedure.* To a solution of the α–sulfonimidoyl β,γ-unsaturated ketone **3b** (R = n-Bu, 0.124 mg, 0.31 mmol) in dry THF (20 mL) was added tetrakis(triphenylphosphine)palladium(0) (0.035 g, 0.031 mmol). The solution was stirred at rt under an atmosphere of nitrogen for 1 h. The solvent was removed *in vacuo* and the yellow orange residue was dissolved in methanol (10 mL). Triethylamine (5 drops) was added and the solution was stirred for 30 min. The solvent was removed *in vacuo*. Purification of the crude product on a short column of silica gel using initially 5% ethyl acetate / hexane and finally 10% ethyl acetate / hexane as eluent gave the title compound as a yellow oil (55 mg, 64 %). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.0-7.4 (m, 5H), 7.00 (dd, J = 15.6, 0.6 Hz, 1H), 6.89 (dd, J = 15.6, 5.2 Hz, 1 H), 4.93 (br d, NH, 1H), 4.43 (br s, CHN, 1H), 3.61 (s, CO_2Me, 3H), 2.0-0.8 (m, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 190.5 (CO), 156.4 (CO), 148.1 (CH), 137.6 (C), 132.8 (CH), 128.54 (CH), 128.51 (CH), 124.9 (CH), 52.5 (OMe), 52.3 (CHN), 34.4 (CH_2), 27.7 (CH_2), 22.3 (CH_2), 13.8 (Me).

Acknowledgment

We thank the Australian Research Council (ARC) for financial support. G. W. O. thanks the ARC and Dunlena Pty. Limited for an APA(Industry) award and Dr. Greg Simpson, CSIRO, for helpful discussions.

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(*Received in UK* 15 *May* 1996; *accepted* 31 *May* 1996)