Tetrahedron Letters, Vol. 34, No. 35, pp. 5627-5630, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

Asymmetric Alkylation of ß-Ketoesters: Synthesis and Michael Additions of a Chiral Sultam-Derived Acetoacetyl Equivalent

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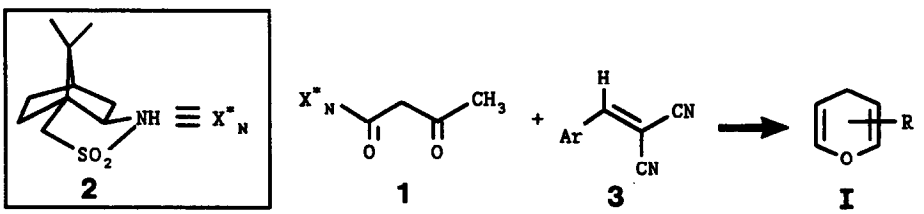
Abstract: *The synthesis and Michael reaction of the chiral acetoacetyl equivalent 1 with arylidenemalononitriles 3 is reported.*

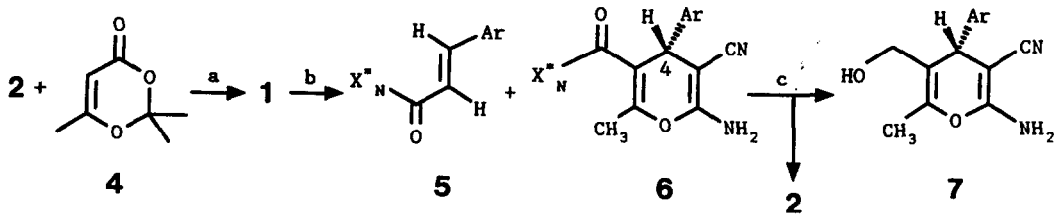
The asymmetric alkylation of ß-ketoesters is a yet unsolved problem of great interest in organic synthesis; only recently several methodological developments have been reported.[1] In our current approach to this subject we have designed the new and chiral sultam-derived acetoacetyl equivalent 1 (Scheme 1), where chirality has been located at the carboxylic part of the ß-ketoester moiety using the well known Oppolzer's sultam 2.[2] In this letter we report the synthesis and asymmetric Michael reaction[3,4] of compound 1 with arylidenemalononitriles 3, eventually leading, after 1,4-addition and *O*-ring closure, to enantiomerically pure 4*H*-pyrans[5,6] (I) (Scheme 1).



Scheme 1

The chiral reagent 1[7] has been synthesized from 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one 4 and 10,2-bornanesultam 2[2] in 86% yield following the standard protocol[8] (Scheme 2). Initial exploratory experiments directed to find the best conditions for the reaction of 1 and 3 (Ar = C_6H_5)[9] gave unsuccessful results using titanium tetrachloride (CH_2Cl_2, -78°C → r.t.)[10], boron trifluoride etherate (CH_2Cl_2, -78°C → r.t.), dimethyl-*t*-butylsilyl triflate (CH_2Cl_2, NEt_3; $TiCl_4$)[11] or LDA (-78°C → r.t.) as promotors or catalysts; using sodium hydroxide under PTC conditions[12], in addition to recovered starting materials, sultam 2, benzaldehyde and N-(*E*-cinnamoyl)-10,2-bornanesultam 5[13] (Ar = C_6H_5) were detected. This compound, as the *E* isomer only, was obtained in 74% yield when sodium hydride (THF; 0°C → r.t.) was used as base. No 4*H*-pyran was observed. Finally, using piperidine as catalyst in toluene,[5,14] compound 1 reacted with 3 giving, after

Michael addition and *O*-ring closure, the expected 4*H*-pyrans **6**[7], in yields and diastereomeric excesses as shown in Table, and traces of the corresponding N-(*E*-3-arylpropenoyl)-10,2-bornanesultams (**5**). From the results in Table we conclude that we have obtained consistent and good values for the d.e.,s (≈60%) in the asymmetric addition of our N-acetoacetyl sultam **1** to the Michael acceptors **3**. These data are also independent of the nature and position of the substituent attached to the phenyl ring in **3**. In the ^{1}H NMR spectra of these diastereomeric mixtures, major and minor isomers **6** showed clearly resolved signals for H-4 at 4.7-4.6 ppm and 4.3-4.2 ppm, respectively. Unfortunately, we were unable to separate these isomers by flash chromatography;[15] only in cases **6a** and **6f** (see Table) we could obtain pure major and minor isomers by recrystallization. After careful analysis of the ^{1}H NMR spectra (see above) of diastereomers **6**, it is clear that in all these cases the major isomer has the same absolute configuration at the new stereocenter (C-4). This stereochemistry has been established as *R* by X-ray diffraction analysis of minor **6a**-(*S*).[16]



a: toluene, 150°C, 82%; b: **3**, piperidine, toluene, r.t.; c: $LiAlH_4$, ether, reflux.

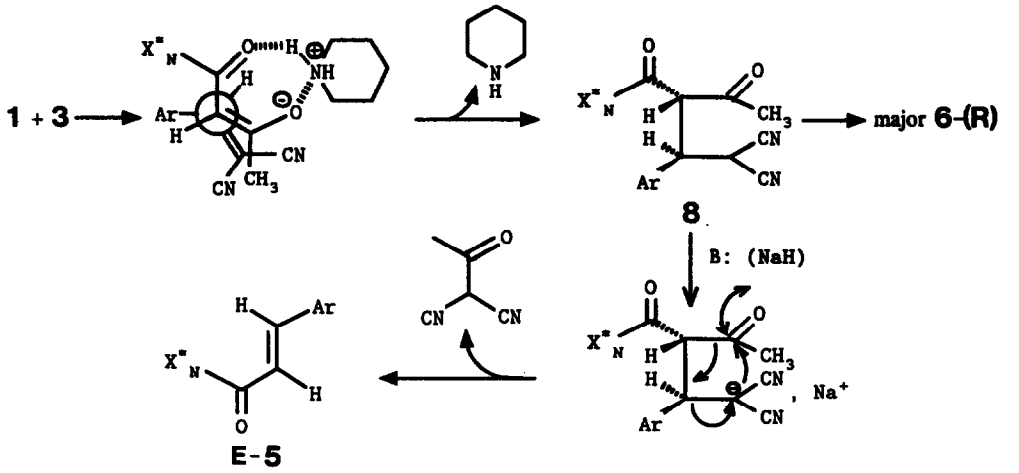
Scheme 2

Table. New 4*H*-pyrans **6** and **7** prepared.

	Ar	6		7
		Yield[1] (%)	d.e.[2] (d.e.)[3]	Yield[1] (%)
a	C_6H_5	65	60 (>99)	73
b	*o*-CH_3-C_6H_4	62	60	72
c	*p*-CH_3-C_6H_4	42	70	59
d	*m*-NO_2-C_6H_4	85	70	40
e	*p*-Br-C_6H_4	91	60	41
f	*p*-Cl-C_6H_4	64	70 (>99)	42

[1] After chromatography. [2] Determined by ^{1}H NMR (300 MHz) on the crude reaction mixtures. [3] After recrystallization.

Finally, after extensive search for optimal conditions[17], pure major isomers **6a**, **6f** and the diastereomeric mixtures **6b-e** were treated with lithium aluminium hydride[14], providing sultam **2** (75-95% yield) and the enantiomerically pure alcohols **7a**[7], **7f**[7] or the enantiomerically enriched alcohols **7b-e** in reasonable yield (see Table).



Scheme 3

The formation of major **6**(*R*) isomers coupled to the exclusive formation of *E*-**5** isomers (traces) during the Michael addition can be explained as shown in Scheme 3. We can assume that the α-unsubstituted acylsultam reacts in a conformation where the carbonyl is *anti* to the SO_2 group[2,18] (also confirmed by X-Ray analysis of compound **1**[16]) and *s-cis* to the Cα,Cß bond due to a presumed internal quelate between the piperidinium cation and the 1,3-dicarbonyl group. The face differentiation is then dictated by the Michael addition to the arylidenemalononitrile from the less hindered bottom face to generate intermediate **8**, that smouthly gives **5** (traces) and **6**. This particular behaviour has also been observed during the 1,4-hydride addition to enoylsultams.[19] As shown, the exclusive formation of *E*-**5** is based on an irreversible intramolecular addition-elimination process. Note that, not surprisingly, in the presence of a stronger base, as sodium hydride (see above), formation of *E*-**5** (Ar = C_6H_5) is preferred to the *O*-ring closure.

The results reported here add to the large panoply of asymmetric syntheses with camphor sultam derivatives and give a clear picture of the power of this chiral auxiliary in order to induce good selectivity in Michael additions. Compound **1** is thus an efficient acetoacetyl chiral equivalent of potential interest in asymmetric synthesis. In addition, with these results, we have improved, in yields and diastereoselectivity, our former experiments[6] in the asymmetric synthesis of multiply functionalized 4*H*-pyrans. Work is now in progress in order to exploit and expand the synthetic usefulness of intermediate **1** and will be reported in due course.

Acknowledgments. Financial support by the Comisión Interministerial de Ciencia y Tecnología of Spain (CICYT, Grants: PB 89-0495 and PB 90-0078) is gratefully acknowledged.

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7. All new compounds have shown good analytical and spectroscopic data: **1**: m.p. 78-81°C; $[\alpha]_D^{25}$ -77.5° (*c* 1.06, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ: 4.00 (d, 1H, *J*=16.8 Hz, CH_2CO), 3.87 (dd, 1H, *J*=7.8 and 4.8 Hz, CHN), 3.66 (d, 1H, *J*=16.8 Hz, CH_2CO), 3.49 (d, 1H, *J*=13.8 Hz, CH_2SO_2), 3.42 (d, 1H, *J*=13.8 Hz, CH_2SO_2), 2.23 (s, 3H, CH_3CO), 2.30-1.85 (5H), 1.45-1.32 (2H), 1.13 (s, 3H, CH_3), 0.95 (s, 3H, CH_3); **6a** (major isomer): m.p. 185-187°C; $[\alpha]_D^{25}$ -165.6° (*c* 0.9, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ: 7.33-7.18 (5H, aromatic), 4.64 (d, 1H, *J*=1.2 Hz, H-4), 4.50 (br s, 2H, NH_2), 3.82 (dd, 1H, *J*=7.8 and 4.8 Hz, CHN), 3.48 (d, 1H, *J*=13.8 Hz, CH_2SO_2), 3.38 (d, 1H, *J*=13.8 Hz, CH_2SO_2), 1.99 (d, 3H, *J*=1.2 Hz, CH_3), 1.93-1.72 (4H), 1.42-1.22 (3H), 1.09 (s, 3H, CH_3), 0.94 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 166.45 (CO), 157.45 (C2), 149.75 (C6), 141.13, 128.49, 127.95, 127.54 (aromatic), 118.91 (CN), 110.35 (C5), 64.29 (CHN), 61.31 (C3), 52.87 (CH_2SO_2), 48.14, 47.60 (2 C), 44.11 (CH), 40.34 (C4), 37.35, 32.45, 26.39 (3 CH_2), 20.44, 19.68, 17.25 (3 CH_3); **7a**: m.p. 95-98°C; $[\alpha]_D^{25}$ +25° (*c* 1.3, CH_3COCH_3); ^1H NMR (300 MHz, CD_3COCD_3) δ: 7.35-7.20 (5H, aromatic), 5.86 (br s, 2H, NH_2), 4.21 (d, 1H, *J*=1.2 Hz, H-4), 4.11 (d, 1H, *J*=12.3 Hz, CH_2OH), 3.60 (d, 1H, *J*=12.3 Hz, CH_2OH), 1.97 (d, 3H, *J*=1.2 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 160.51 (C2), 144.23 (C6), 145.30, 129.26, 128.77, 127.67 (aromatic), 120.46 (CN), 113.36 (C5), 59.63 (C3), 59.03 (CH_2OH), 40.53 (C4), 15.44 (CH_3); **7f**: m.p. 111-113°C ; $[\alpha]_D^{25}$ +37.6° (*c* 1.23, CH_3OH); ^1H NMR (300 MHz, $CDCl_3$) δ: 7.30 (td, 2H, aromatic), 7.18 (td, 2H, aromatic), 4.56 (br s, 2H, NH_2), 4.18 (d, 1H, *J*=0.9 Hz, H-4), 4.07 (d, 1H, *J*=12.3 Hz, CH_2OH), 3.74 (d, 1H, *J*=12.3 Hz, CH_2OH), 1.98 (d, 3H, *J*=0.9 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 158.71 (C2), 144.61 (C6), 141.58, 133.14, 129.22, 128.90 (aromatic), 119.44 (CN), 111.28 (C5), 60.46 (C3), 59.71 (CH_2OH), 39.34 (C4), 15.34 (CH_3).
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14. General procedure for the synthesis of **6** and **7**: Compound **1** (1.0 equiv) was dissolved in dry toluene, and piperidine (four drops) plus the appropriate arylidenemalononitrile **3** (1.5 equiv) were added. The solution was stirred at r.t. for 24-48 h. The solvent was removed and the residue submitted to FC giving compound **6**. A solution of **6** (1.0 equiv) in THF/ether (1:5, 18 mL/0.5 mmol) was added to a stirred suspension of $LiAlH_4$ (2.5 equiv) in dry ether (4 mL/mmol) at 0°C. Stirring (0°C, 3h), addition of saturated aqueous NH_4Cl, extraction with ether, drying, concentration and FC gave the recovered sultam **2** (75-95% yield) and the alcohol **7**.
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(Received in UK 19 May 1993; accepted 9 July 1993)