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Stereoselective Mannich reaction of camphor titanium enolate

Sergio Pinheiro,[a,*] Sandro J. Greco,[a] Leandro S. Veiga,[a] Florence M. C. de Farias[a] and Paulo R. R. Costa[b]

[a]*LASA, Instituto de Química, Universidade Federal Fluminense, CEG, Centro, 24210-150 Niterói, RJ, Brazil*
[b]*LQB, Núcleo de Pesquisas de Produtos Naturais, Universidade Federal do Rio de Janeiro, CCS, 21941-590 Rio de Janeiro, RJ, Brazil*

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Abstract—The Mannich reaction of the titanium enolate derived from D-camphor with different electrophiles leading stereoselectively to the *exo* adduct has been performed using an attractive procedure. © 2002 Published by Elsevier Science Ltd.

1. Introduction

The Mannich reaction is the classical methodology for the preparation of β-amino ketones. These Mannich bases and related compounds are versatile synthetic intermediates to access many interesting structures[1] including natural products and pharmacologically active compounds.[2,3]

Modern variants of the Mannich reaction, whose range of application is much wider than the classical method (CH_2O+$Me_2NH{\cdot}HCl$), can be performed with effective control of the regio- and stereochemistry using iminium salts, imines, aminals and *N*,*O*-acetals as electrophiles.[4,5] Although the classical conditions are not applicable to the hindered D-camphor,[6,7] the reaction of its potassium enolate with Eschenmoser's salt gives a mixture of the *endo* and *exo* adducts (60% yield, *endo*:*exo* = 4:1), from which the thermodynamic *endo* isomer is obtained by repeated recrystallization from pentane.[6] Due to the high basicity of potassium enolates, where epimerization favors the *endo* adduct, the method reported to form the *exo* isomer (86% yield crude, *exo*:*endo* = 97:3) involves addition of the trimethylsilyl enol ether derived from D-camphor to Eschenmoser's salt.[6,8] Conversely, the addition of both lithium and boron enolates derived from camphor to aminals gives a mixture of *endo* and *exo* adducts, from which the stereoselectivities were not determined.[9]

Titanium enolates have been successfully added to activated imines, *N*-acyloxy iminium and cyclic *N*-acyl iminium salts.[10–12] Herein, we report that the stereoselective Mannich reactions of the titanium enolate of D-camphor with iminium salts, aminals and *N*,*O*-acetals lead to *exo* adducts by means of a simple and very attractive procedure.

2. Results and discussion

The titanium enolate of D-camphor was generated using a 1 M solution of $TiCl_4$ in dichloromethane and *N*,*N*-diisopropylethylamine at −10°C (Table 1).[13] The addition of this intermediate to Eschenmoser's salt led mainly to the adduct *exo* **1a** in satisfactory yield (entry 1). The isomer obtained has identical NMR spectra to the *exo* adduct **1a** already described by Mosher and co-workers,[6] and the minor isomer, *endo*-**2a**, can be removed by crystallization of the mixture as reported by these authors. The reaction of the D-camphor titanium enolate with pyrrolidylmethylene ammonium chloride[14] furnished the *exo* adduct **1b** as the major product (entry 2). The lower *exo*:*endo* ratio observed in this case is in agreement with the better diastereoselectivity reported for the reaction of the trimethylsilyl enol ether derived from D-camphor with Eschenmoser's salt (an iodide) when compared with the use of $CH_2{=}NMe_2^+Cl^-$ as the electrophile.[6] In contrast to the formation of mixture of *exo* and *endo* adducts in the addition of both lithium and boron enolates derived from D-camphor to aminals,[9] the Mannich reaction of the D-camphor titanium enolate with *N*,*N*-dipyrrolidinemethane[15] led selectively to the *exo* adduct

* Corresponding author. Fax: 5521-27193349; e-mail: spin@rmn.uff.br

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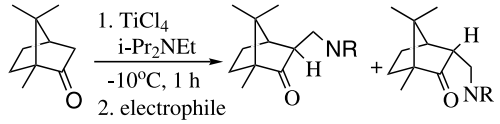
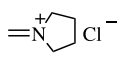
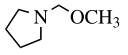
Table 1. Stereoselective Mannich reaction of D-camphor titanium enolate



D-camphor **1** **2**

a: R = $(CH_3)_2$; **b**: R = $(CH_2)_4$

Entry	Electrophile [a]	Adduct	Yield % [b]	**1** : **2** [c]
1	$=\overset{+}{N}(CH_3)_2\ I^-$	**a**	52	95 : 5 [d]
2		**b**	41	91 : 9
3		**b**	33	89 : 11
4		**b**	50	92 : 8

[a] Reactions were performed at 1.0 g (6.57 mmol) scale of D-(+)-camphor.

[b] Yields of the purified mixture of adducts **1** and **2**.

[c] Determined by ^{1}H NMR spectra (300 MHz) via the relative integration of the CH_3 signals unless noted.

[d] Determined by the relative integration of signals for the C=O carbon in quantitative ^{13}C NMR.

1b, though in low yields (entry 3).[5g] This isomer was also obtained in moderate yield and satisfactory stereoselectivity by the use of *N*-methoxy (methylene) pyrrolidine as the electrophile (entry 4).[14]

All signals in the ^{1}H NMR spectrum of the mixture of **1a** and **2a** are too close together for the purposes of determining the diastereomeric ratio of the product, so the stereoselectivity of these reactions was determined from the relative intensities of the signals due the carbonyls carbons at 223.0 and 222.5 ppm, respectively, in the quantitative ^{13}C NMR spectra employing the 'gated decoupled' procedure. The ratios of **1b** and **2b** in the mixtures were determined from the signals of the methyl groups at 1.01 ppm (for **2b**) and 0.94 ppm (for **1b**) in the crude ^{1}H NMR spectra and confirmed by the signals of the carbonyl carbons in the quantitative ^{13}C NMR spectra.

The stereochemical assignment of the main adduct **1b** was made on the basis of NOE NMR spectra (Fig. 1). Thus, no NOE effect was observed for the methyl groups with the signal attributed to H-3 at 2.12 ppm, suggesting an *exo* configuration for the main isomer. For the hydrogen H-8 a significant NOE value was observed with H-11 (2.4%). The hydrogen H-9 exhibited an NOE effect with H-5β (1.8%) and H-11 showed an NOE effect with H-8 (1.8%), allowing the assignment of the signals due to H-8, H-9 and H-10 in the ^{1}H NMR spectrum.

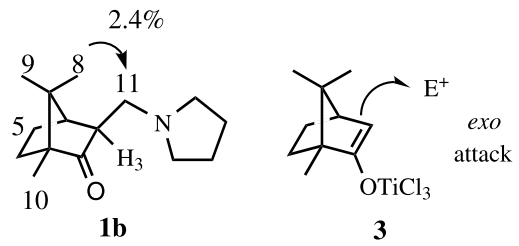


Figure 1. Stereochemical assignment of **1b** and *exo* attack on the enolate.

The formation of the *exo* adducts **1a** and **1b** from D-camphor titanium enolate **3** under non-equilibrating conditions can be explained by the preferential *exo* attack of the electrophile. Indeed, this stereochemical pathway is in agreement with the results reported for the aldol addition reaction of the D-camphor lithium enolate.[16]

3. Conclusion

In summary, the use of the D-camphor-derived titanium enolate offers a one pot alternative to the use of the trimethylsilyl enol ether[6] to access *exo* adducts using the Mannich reaction. In addition, this is a complementary method to the use of the D-camphor potassium enolate for preparation of the *endo* adduct.

4. Experimental

4.1. General

N,*N*-Diisopropylethylamine and CH_2Cl_2 were distilled from CaH_2. Reactions were carried out under an inert atmosphere (N_2). Optical rotations were recorded with a Perkin–Elmer 24B polarimeter. Infra-red spectra were recorded with a Perkin–Elmer 1420. High-resolution (HREIMS) and low-resolution electron impact mass spectra (LREIMS) were measured on a VG Auto Spec. Q. NMR spectra were recorded with a Varian VXR 300.

4.2. Typical procedure for the Mannich reaction

To a solution of (1*R*)-(+)-camphor (1.0 g, 6.57 mmol) in dry dichloromethane (33 mL) under a nitrogen atmosphere was added dropwise a solution of $TiCl_4$ in CH_2Cl_2 (1 M, 7.23 mmol). The solution was stirred for 15 min, *N*,*N*-diisopropylethylamine (0.9345 g, 7.23 mmol) was added and the mixture was stirred at −10°C for 1 h. The resulting solution was added dropwise to a −10°C cooled mixture of the appropriate electrophile (7.23 mmol, as indicated in Table 1) in CH_2Cl_2 (7.3 mL), the mixture was allowed to reach room temperature and stirred overnight. The reaction was quenched with satd NH_4Cl (30 mL) and water (30 mL). The phases were separated, the aqueous layer was extracted with ethyl acetate (3×50 mL) and the combined organic layers were concentrated. In all cases the usual acidic purification gave mixtures of the adducts **1a**,**b** and **2a**,**b** as pale yellow oils in the yields shown in Table 1.

Adducts **1b** and **2b** (*exo*+*endo*) in 82% d.e. $[\alpha]_D^{25}$ +46.2 (*c* 5, CH_2Cl_2). IR (neat, cm^{-1}): 2958, 2788, 1741, 1449, 1370, 1324, 1147, 1020, 884, 666. ^1H NMR ($CDCl_3$, 300 MHz, COSY, ppm): 2.86 (dd, $J_{11A\text{-}11B}=12.5$ Hz, $J_{11A\text{-}3}=4.5$ Hz, $J_{11B\text{-}3}=3.2$ Hz, H-11 of **1b**), 2.75 (dd, $J_{11A\text{-}11B}=12.5$ Hz, $J_{11A\text{-}3}=6.2$ Hz, $J_{11B\text{-}3}=4.5$ Hz, H-11 of **2b**), 2.64–2.56 (m, H-11 and H-12), 2.26–2.22 (m, H-3 and H-4 of **2b**), 2.14 (d, $J_{4\text{-}5\beta}=3.9$ Hz, H-4 of **1b**), 2.12 (dd, $J_{3\text{-}11A}=4.5$ Hz, $J_{3\text{-}11B}=3.2$ Hz, H-3 of **1b**), 2.05–1.96 (m, H-5β), 1.88–1.79 (m, H-13), 1.70–1.59 (m, H-5α), 1.55–1.40 (m, H-6α and H-6β), 1.01 (s, CH_3 of **2b**), 0.94 (s, CH_3 of **1b**), 0.90 (s, CH_3 of **1b**), 0.89 (s, CH_3 of **2b**), 0.77 (s, CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz, DEPT, HETCOR, ppm): 219.7 (C-2 of **1b**), 219.6 (C-2 of **2b**), 58.0 (C-11 of **2b**), 57.4 (C-11 of **1b**), 56.7 (C-1), 54.1 (C-3 of **1b**), 53.9 (C-3 of **2b**), 53.6 (C-12 of **1b**), 52.7 (C-12 of **2b**), 49.5 (C-4 of **2b**), 47.6 (C-4 of **1b**), 46.2 (C-7 of **1b**), 45.3 (C-7 of **2b**), 30.5 (C-5 of **2b**), 28.8 (C-5 of **1b**), 28.3 (C-6), 22.9 (C-13 of **1b**), 20.9 (CH_3 of **1b**), 20.0 (C-13 of **2b**), 19.7 (CH_3 of **1b**), 19.0 (CH_3 of **2b**), 18.7 (CH_3 of **2b**), 9.0 (CH_3 of **2b**), 8.8 (CH_3 of **1b**). LREIMS (70 eV, *m*/*z*): 237 (M+2, 3), 236 (M+1, 15), 235 (M^+, 12), 84 (100), 55 (21). HREIMS calcd for $C_{15}H_{25}NO$ (M^+): 235.3650. Found: 235.3882.

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