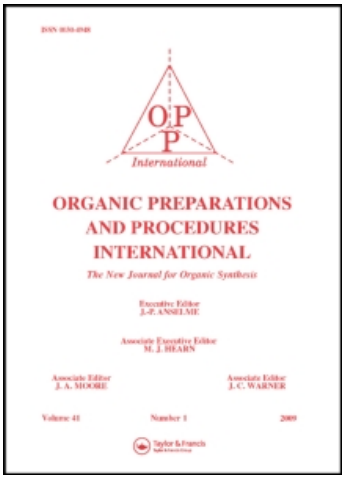

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TREATMENT OF CONJUGATED AZOALKENES WITH N-ACYL-N'-TOSYLHYDRAZIDES. A USEFUL ENTRY TO ASYMMETRIC bis-ACYLHYDRAZONES

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TREATMENT OF CONJUGATED AZOALKENES WITH N-ACYL-N'-TOSYLHYDRAZIDES. A USEFUL ENTRY TO ASYMMETRIC bis-ACYLHYDRAZONES

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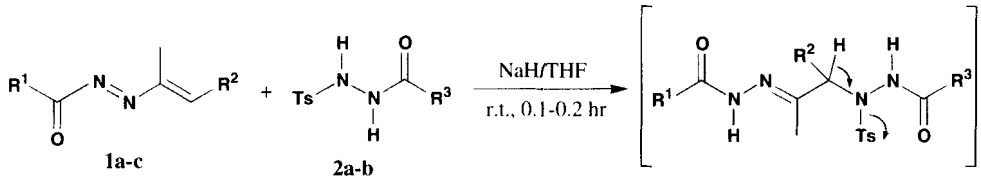
In continuation of our studies in the synthetic usefulness[1-3] of conjugated azoalkenes we wish to report the one-pot reaction between some alkoxy- and aminocarbonylazoalkenes with N-acyl-N'-tosylhydrazides to yield new asymmetric *bis*-acylhydrazones.

N-Acyl-N'-tosylhydrazides **2a-b** where treated with a stoichiometric amount of sodium hydride, reacted smoothly in tetrahydrofuran at room temperature (0.1-0.2 hr) by attack by the tosyl-NH group on the *azo-ene* system of conjugated azoalkenes **1a-c**. Asymmetric *bis*-acylhydrazones **3a-f** were obtained in good to excellent yields (76-95%), by ready loss of *p*-toluenesulfinic acid without isolation of intermediates. To avoid the problem resulting from competitive nucleophilic attack by the *p*-toluenesulfinic acid on the heterodiene system of the conjugated azoalkenes, a molar ratio 2:1 between reagents **1** and **2**, respectively, was used.

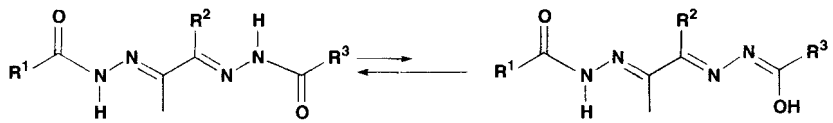
Products **3c**, **3d** and **3f**, isolated as isomeric mixtures, exhibited a *keto-enol* tautomeric equilibrium, **3a** and **3e** were present only in the *keto* form while **3b** was detected only in the *enol* form. Reaction times, yields and melting points of *bis*-acylhydrazones **3a-f** are summarized in the Table.



1a-c **2a-b**

1a) R^1 = MeO, R^2 = CO_2Me
1b) R^1 = PhNH, R^2 = CO_2Me
1c) R^1 = *t*-BuO, R^2 = CO_2Me

2a) R^3 = Me
2b) R^3 = Ph



3a-f **3a-f**

3a) R^1 = MeO, R^2 = CO_2Me, R^3 = Me **3b**) R^1 = MeO, R^2 = CO_2Me, R^3 = Ph
3c) R^1 = PhNH, R^2 = CO_2Me, R^3 = Me **3d**) R^1 = PhNH, R^2 = CO_2Me, R^3 = Ph
3e) R^1 = *t*-BuO, R^2 = CO_2Me, R^3 = Me **3f**) R^1 = *t*-BuO, R^2 = CO_2Me, R^3 = Ph

TABLE. Preparation of *bis*-Acylhydrazones **3a-f**.

Reactants 1	2	Products 3	Yield[a] (%)	Time (hrs)	mp[b] (°C)
1a	**2a**	**3a**	79	0.1	204-215
1a	**2b**	**3b**	95	0.2	160-161
1b	**2a**	**3c**	76	0.2	175-181
1b	**2b**	**3d**	92	0.2	194-195
1c	**2a**	**3e**	82	0.1	182-188
1c	**2b**	**3f**	78	0.1	162-163

a) Yield of isolated product **3** based on **2**. b) Uncorrected, measured on a Büchi (Dr. Tottoli) apparatus, often occurs with decomposition.

This method constitutes a convenient and inexpensive one-pot procedure that allows the synthesis of products useful for a wide range of applications (i. e. conjugated additions,[4] cycloadditions and annulations,[5] ligands for transition metals,[6] etc.). Indeed it is known that aroylhydrazones and their parent hydrazines have tuberculostatic activity which has been attributed to their ability to form stable chelates with certain transition metals present in the cell.[7]

EXPERIMENTAL SECTION

Conjugated azoalkenes **1a-c** were prepared as previously reported.[8,9] N-acyl-N'-tosylhydrazides **2a-b** were synthesized by usual methods from the literature. Melting points were determined in open capillary tubes on a Büchi apparatus and are uncorrected. The products often decompose at their melting point. IR spectra were obtained as Nujol mulls on a Perkin-Elmer 298 spectrophotometer. ^{1}H NMR spectra at 200 MHz were recorded on a Bruker AC-200 spectrometer and performed in DMSO-d_6. Chemical shifts (δ) are reported in ppm downfield from internal TMS. Macherey-Nagel precoated silica gel SIL G-25UV$_{254}$ plates (0.25 mm) were employed for analytical thin layer chromatography (TLC) and Baker silica gel (0.063-0.200 mm) for column chromatography.

Synthesis of *bis*-Acylhydrazones (3a-f). Typical Procedure.- To a well stirred solution of N-acyl-N'-tosylhydrazides **2a-b** (1 mmol) dissolved in THF (4 mL) was added sodium hydride (1 mmol) and the mixture was stirred at room temperature for 5 min. To this cloudy grey solution were added dropwise (2 min) azoalkenes **1a-c** (2 mmol) dissolved in THF (10 mL). The orange-red color of the azoalkene disappeared rapidly and the mixture turned to pale yellow. After the evaporation of the reaction solvent, the crude reaction product was purified by column chromatography (cyclohexane-ethyl acetate or dichloromethane-ethyl acetate mixtures) to afford a mixture of isomeric products **3a-f**, mainly in the *keto* form, with traces of *enol* form. Only in the case of product **3f** was it possible to separate the *keto* from the *enol* forms by column chromatography. *bis*-Acylhydrazones **3a-f** crystallized from dichloromethane/petroleum ether.

3a: IR: 3390, 3210, 3130, 1740, 1700, 1680, 1600, 1580 cm^{-1}; ^{1}H NMR: δ 2.04 and 2.19 (2s, 6H, 2xCH$_3$), 3.69 and 3.77 (2s, 6H, 2xOCH$_3$), 10.49, 11.00 and 11.24 (3s, 2H, 2xNH, D$_2$O ex) ppm.

Anal. Calcd. for $C_9H_{14}N_4O_5$: C, 41.86; H, 5.46; N, 21.70. Found: C, 41.78; H, 5.48; N, 21.85

3b: IR: 3470, 3250, 3220, 1740, 1730, 1625, 1600, 1570 cm^{-1}; ^1H NMR: δ 2.07 (s, 3H, CH_3), 3.75 and 3.84 (2s, 6H, 2xOCH_3), 7.51-7.70 (m, 3H_{arom}), 8.04 (d, 2H_{arom}, *J*= 7.0 Hz), 10.94 (s, 1H, NH, D_2O ex), 13.78 (br s, 1H, OH, D_2O ex) ppm.

Anal. Calcd. for $C_{14}H_{16}N_4O_5$: C, 52.50; H, 5.03; N, 17.49. Found: C, 52.47; H, 5.10; N, 17.32

3c: IR: 3340, 3320, 3200, 1720, 1705, 1690, 1600, 1575, 1540 cm^{-1}; ^1H NMR: δ 2.08 and 2.23 (2s, 6H, 2xCH_3), 3.80 (s, 3H, OCH_3), 7.01 (t, 1H_{arom}, *J* = 7.0 Hz), 7.54 (d, 2H_{arom}, *J* = 7.0 Hz), 8.94 (s, 1H, NH, D_2O ex), 9.96 (s, 1H, NH, D_2O ex), 12.03 and 12.85 (s and br s, 1H, NH and OH, D_2O ex) ppm.

Anal. Calcd. for $C_{14}H_{17}N_5O_4$: C, 52.66; H, 5.37; N, 21.93. Found: C, 52.58; H, 5.29; N, 22.05

3d: IR: 3280, 3210, 3130, 1720, 1690, 1670, 1595, 1540, 1530 cm^{-1}; ^1H NMR: δ 2.10 (s, 3H, CH_3), 3.86 and 3.93 (2s, 3H, OCH_3), 7.04 (t, 1H_{arom}, *J* = 7.0 Hz), 7.08-7.55 (m, 7H_{arom}), 8.12 (d, 2H_{arom}, *J* = 7.0 Hz), 8.53 and 9.46 (2s, 1H, NH, D_2O ex), 10.32 (s, 1H, NH, D_2O ex), 11.77 and 13.63 (s, and br s, 1H, NH and OH, D_2O ex) ppm.

Anal. Calcd. for $C_{19}H_{19}N_5O_4$: C, 59.84; H, 5.02; N, 18.36. Found: 59.79; H, 4.96; N, 18.56

3e: IR: 3480, 3210, 3110, 1755, 1690, 1675, 1610 cm^{-1}; ^1H NMR: δ 1.45 (s, 9H, *t* -BuO), 2.00 and 2.18 (2s, 6H, 2xCH_3), 3.76 (s, 3H, OCH_3), 10.15 (s, 1H, NH, D_2O ex), 10.93 and 11.19 (2s, 1H, NH, D_2O ex) ppm.

Anal. Calcd. for $C_{12}H_{20}N_4O_5$: C, 47.99; H, 6.71; N, 18.66. Found: C, 47.88; H, 6.82; N, 18.70

3f (keto form): IR: 3220, 3180, 1755, 1740, 1710, 1660, 1600, 1580, 1540, 1530 cm^{-1}; ^1H NMR: δ 1.45 (s, 9H, *t* -BuO), 2.01 (s, 3H, CH_3), 3.79 (s, 3H, OCH_3), 7.49-7.53 (m, 3H_{arom}), 7.71 (d, 2H_{arom}, *J* = 7.0 Hz), 10.22 (s, 1H, NH, D_2O ex), 11.60 (s, 1H, NH, D_2O ex) ppm.

Anal. Calcd. for $C_{17}H_{22}N_4O_5$: C, 56.35; H, 6.12; N, 15.46. Found: C, 56.48; H, 6.28; N, 15.45

3f (enol form): IR: 3440, 3220, 1735, 1680, 1600, 1580, 1530, 1510 cm^{-1}; ^1H NMR: δ 1.49 (s, 9H, *t* -BuO), 2.05 (s, 3H, CH_3), 3.83 (s, 3H, OCH_3), 7.46-7.65 (m, 3H_{arom}), 8.09 (d, 2H_{arom}, *J* = 7.0 Hz), 10.71 (s, 1H, NH, D_2O ex), 13.94 (br s, 1H, OH, D_2O ex) ppm.

Anal. Calcd. for $C_{17}H_{22}N_4O_5$: C, 56.35; H, 6.12; N, 15.46. Found: C, 56.42; H, 6.19; N, 15.25

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A HIGHLY STEREOSELECTIVE TRANSFORMATION OF β-SANTALENE TO (E)-β-SANTALOL

Submitted by (07/06/93)

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The great fixative properties and woody-sweet odor of East Indian Sandalwood oil are mainly due to α- and β-santalols (**1** and **2**) which constitute more than 90% of the oil.[1,2] Several minor components of the oil such as β-santalene (**3**), *epi*-β-santalene, *epi*-β-santalol also contribute to the perfuming properties to a lesser extent.[3] The synthesis of santalols, santalenes and other fragrance compounds of the sandalwood type has been reported.[4-6] We now describe a highly regio- and stereoselective transformation of β-santalene (**3**) to (E)-β-santalol (**4**) by an N-oxide [2,3]sigmatropic rearrangement.[7]