Lewis-acid Catalysed Tandem Reaction Diels–Alder–[3,3] Sigmatropic Shift between Buta-1,3-dienyl Thiocyanic Acid Ester and Acryloyl Chloride: Application in the Synthesis of 2-Azabicyclo[2.2.2]oct-5-ene Derivatives.

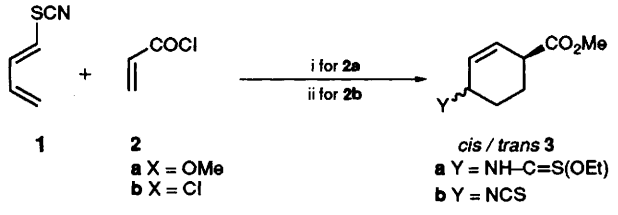
Joseph Schoepfer, Christian Marquis, Cécile Pasquier and Reinhard Neier*

Institute of Chemistry, University of Neuchâtel, Avenue de Bellevaux 51, CH-2000 Neuchatel, Switzerland

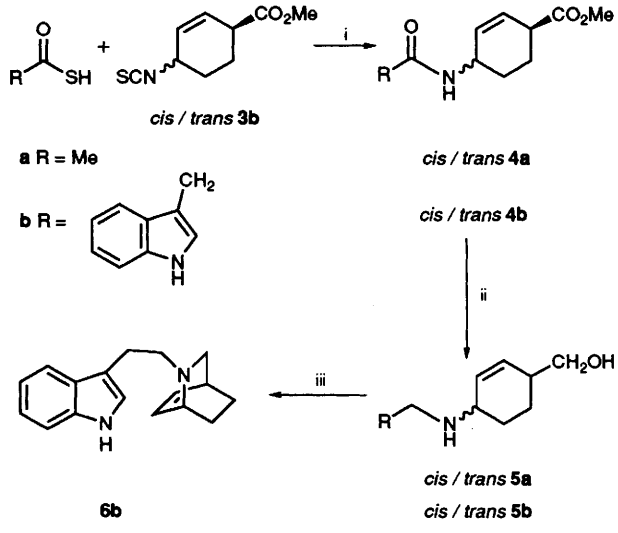
Buta-1,3-dienyl thiocyanic acid ester reacts with acryloyl chloride in presence of Lewis acid catalysts to produce directly the rearranged product of type **3b** *via* a combination of a Diels–Alder reaction with a [3,3] sigmatropic shift; the 1,4-substituted cyclohexene is easily transformed into the 2-azabicyclo[2.2.2]oct-5-ene derivative **6b**, which has been used as precursor for the synthesis of the Ibogamin skeleton.

Combining two or several reaction steps into a one-pot reaction has become an attractive goal for the synthetic organic chemist.[1,2] The tandem Diels–Alder reaction and [3,3] sigmatropic shift between the easily accessible buta-1,3-dienyl thiocyanic acid ester **1**[3,4] and appropriate dienophiles in ethanol yields 1,4-substituted cyclohexenes.[3,5] The tandem reaction between methyl acrylate **2a** and the diene **1** in ethanol forms the thiocarbamate **3a** (Scheme 1). The goal of this work was to use the product **3a** as precursor for the preparation of the skeleton of Iboga-type alkaloids.[6] The transformations of the thiocarbamate **3a** proved to be difficult, which led us to develop a Lewis acid catalysed version of the tandem reaction in toluene as solvent, yielding directly the isothiocyanate **3b** (Scheme 1). The isothiocyanate **3b** was transformed in three steps into the 2-azabicyclo[2.2.2]oct-5-ene **6b** (Scheme 2), which has been used by Trost *et al.* for the synthesis of desethylibogamin.[6]

As the buta-1,3-dienyl thiocyanic acid ester **1** reacts as a strongly deactivated diene, highly activated dienophiles are required.[3,5] The diene **1** reacted in the trandem reaction with acryloyl chloride **2b** and the product was treated with methanol in the presence of triethylamine to give the corresponding methyl ester **3b** (Scheme 1). Good yields of the cycloadduct could only be obtained if the reaction was catalysed with Lewis acids like $AlCl_3$, $TiCl_4$ and $BF_3{\cdot}OEt_2$ in the presence of small quantities of 2,6-di-*tert*-butyl-*p*-cresol (BHT) as radical trap (Table 1). Use of $TiCl_4$ was advantageous because smaller quantities of catalyst (6 instead of 10 mol%) were needed. However the best yields (84%) were obtained using $BF_3{\cdot}OEt_2$ in toluene at 50 °C.† Moreover carrying out the tandem reaction at temperatures below 50 °C gave a better ratio of the *cis : trans* diastereoisomers (90 : 10) than in the earlier version of the tandem reaction.[3,5]



Scheme 1 *Reagents and conditions*: i, BHT, EtOH, 110 °C, 60%; ii, cat., toluene then MeOH, Et_3N



Scheme 2 *Reagents and conditions*: i, benzene, reflux, **4a** 73%, **4b** 71%; ii, $LiAlH_4$, THF, reflux, **5a** 88%, **5b** 82%; iii, PPh_3, CCl_4, Et_3N, acetonitrile, reflux, **6b** 25%

Treatment of the isothiocyanate **3b** with thioacetic acid, or with indolylthioacetic acid gave the amides **4a** and **b** respectively in good yield. The attribution of the relative configuration of the diastereoisomers was mainly based on the ^1H NMR spectra. X-Ray analysis of *cis*-**4a** confirmed the structure and the relative configuration deduced from the ^1H NMR spectra. The amides **4a** and **b** were reduced with $LiAlH_4$ to the amino alcohols **5a** (88%) and **b** (82%). Compound **5b** was transformed into the desired bicycle **6b** with CCl_4 and triphenylphosphine. Although the transformation was complete only a moderate yield (25%) of the spectroscopically pure product **6b** could be isolated, due to difficulties in separation of the product from the formed by-product triphenylphosphine oxide.

The tandem reaction Diels–Alder reaction–[3,3] sigmatropic shift can be used for the synthesis of 2-azabicyclooctenes like **6b**. In the newly developed Lewis acid catalysed variant the activation probably occurs on the acryloyl chloride. The tandem reaction between buta-1,3-dienyl thiocyanic acid ester **1** and acryloyl chloride **2b** in toluene leads directly to 1,4-substituted cyclohexene derivatives, with the correct substitution pattern.

We acknowledge financial support from Swiss National

Table 1 Results of the catalysed tandem reaction of buta-1,3-dienyl thiocyanic acid ester **1** with acryloyl chloride **2b** in toluene

Catalyst[a]	*T*/°C	*t*/h	Yield (%) *cis–trans* **3b**[b]	Diastereoisomeric ratio[c]
—	110	18	60 (**3a**)[d]	70 : 30
Molecular sieves	25	161	32	79 : 21
$AlCl_3$	110	44	35	44 : 56
$TiCl_4$	25	24	46	70 : 30[e]
$TiCl_4$[f]	0–25	90	57	80 : 20[e]
$BF_3{\cdot}OEt_2$	25	504	65	90 : 10
$BF_3{\cdot}OEt_2$	50	72	84	85 : 15

[a] 0.1 Equiv. [b] Pure substance after flash chromatography. [c] *Cis : trans* ratio determined from the ^1H NMR spectrum of the pure substance. [d] Reaction of methyl acrylate **2a** with **1** in EtOH. [e] The diastereoisomeric ratio was determined with GC. [f] Only 0.06 equiv. of catalyst were used.

Foundation. We thank Professor Dr H. Stoeckli-Evans for the X-ray analysis of compound *cis*-**4a**.

Received, 30th December 1993; Com. 3/07622I

Footnote

† *Cis–trans*-**3b**: A solution of **1**[3,5] (3.0 g, 27 mmol), acryloyl chloride **2b** (7.33 g, 81 mmol), $BF_3{\cdot}OEt_2$ (383 mg, 2.7 mmol) and BHT (20 mg, 0.1 mmol) in dry toluene (50 ml) was kept for 78 h at 50 °C under nitrogen. The solution was cooled to room temp., methanol (8 ml) and triethylamine (8 g, 79 mmol) were added. The solution was diluted with diethyl ether, washed with water, dried with magnesium sulfate, filtered and the solvent was evaporated. The crude product was purified by chromatography (silica gel, hexane–ethyl acetate 4 : 1) and yielded *cis–trans*-**3b** as colourless oil (4.456 g, 84%) in a diastereoisomeric ratio of 85 : 15.

cis-**3b**: oil; δ_H (400 MHz, $CDCl_3$) 6.04 (ddd, $^3J_{H,H}$ 9.9, $^3J_{H,H}$ 2.8, $^4J_{H,H}$ 1.3, 1 H, =CH), 5.83 (dm, $^3J_{3,2}$ 9.9, 1 H, =CH), 4.25–4.22 [m, 1 H, CH(N–)], 3.72 (s, 3 H, OCH_3), 3.08–3.03 [m, 1 H, $CH(CO_2–)$], 2.08–1.97 and 1.95–1.85 (m, 4H, CH_2CH_2); δ_C 173.5, 133.2, 129.6, 127.2, 52.8, 52.1, 41.2, 29.0 and 22.0.

trans-**3b**: oil; δ_H (400 MHz, $CDCl_3$) 5.99 (ddd, $^3J_{H,H}$ 10.0, $^3J_{H,H}$ 3.2, $^4J_{H,H}$ 1.8, 1 H, =CH), 5.83 (dm, $^3J_{3,2}$ 10.0, 1 H, =CH), 4.27–4.25 [m, 1 H, CH(N–)], 3.70 (s, 3 H, OCH_3), 3.19–3.14 [m, 1 H, $CH(CO_2–)$], 2.19–2.13, 2.10–2.03 and 1.93–1.80 (m, 4H, CH_2CH_2); δ_C 173.8, 133.1, 129.2, 127.7, 52.8, 52.6, 41.0, 29.2 and 22.7.

References

1 L. F. Tietze and U. Beifuss, *Angew. Chem.*, 1993, **105**, 137; *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 131.
2 T. L. Ho, *Tandem Organic Reactions*, Wiley, New York, 1992.
3 S. Huber, P. Stamouli and R. Neier, *J. Chem. Soc., Chem. Commun.*, 1985, 533.
4 J. Schoepfer, E. Eichenberger and R. Neier, *J. Chem. Soc., Chem. Commun.*, 1993, 246.
5 S. Huber, P. Stamouli, T. Jenny and R. Neier, *Helv. Chim. Acta*, 1986, **69**, 1898.
6 B. M. Trost and J. P. Genêt, *J. Am. Chem. Soc.*, 1976, **98**, 8516; B. M. Trost, S. A. Goldeski and J. P. Genêt, *J. Am. Chem. Soc.*, 1978, **100**, 3930; B. M. Trost and E. Keinan, *J. Am. Chem. Soc.*, 1978, **100**, 7779.