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Nazarov Cyclisation of Dienone-Esters and Tetrahydropyrones using Trimethylsilyltriflate

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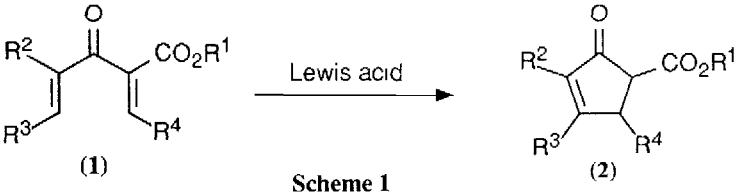
Key Words: Nazarov Cyclisation; Trimethylsilyltriflate; Dienone; Tetrahydropyrone; Knoevenagel Condensation.

Abstract: *Cyclopentenone esters have been synthesized via a Nazarov cyclisation of the corresponding α,α'-dienone esters or tetrahydro-γ-pyrone esters employing trimethylsilyltriflate at room temperature. The dienone esters were synthesised by a short two-step acylation-Knoevenagel sequence.*

A potentially very useful variant upon the classical Nazarov cyclisation[2,3] is one in which the product cyclopentenone contains a functional group suitably sited for subsequent molecular elaboration. Incorporation of an alkoxycarbonyl moiety into Nazarov substrates (**1**), which were synthesised via [α-(carboethoxy)vinyl]cuprate methodology, has been described by Marino,[3e] together with their cyclisation to cyclopentenones (**2**) using various Lewis acids (Scheme 1). The ester group also effectively controls the position of the double bond in (**2**), which is often a problem in the classical cyclisation.



(**1**) (**2**)

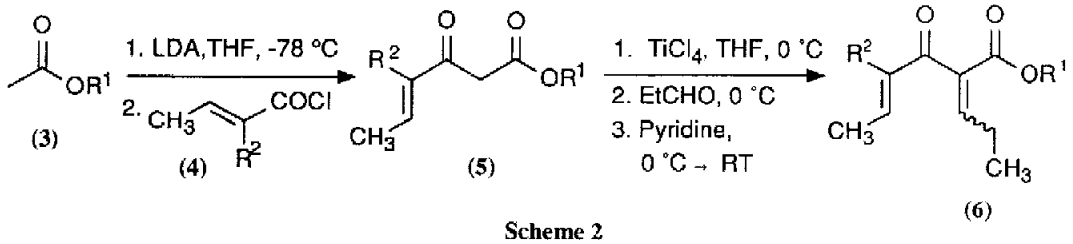
Scheme 1

Whilst researching into the possibility of effecting asymmetric induction via the incorporation of a chiral auxiliary moiety as an ester appendage, we found Marino's route to be incompatible with esters of very bulky chiral alcohols (in particular (-)-menthol and (+)-camphor derivatives[4]). Thus the following acylation-Knoevenagel sequence was developed as a general route to Nazarov cyclisation precursors.

Acylation of the lithium enolates of various acetate esters (**3**) with α,β-unsaturated acid chlorides (**4**) proceeded satisfactorily using the conditions described by Rathke[5] (Scheme 2). No 1,4-addition was observed within the limits of t.l.c. and n.m.r. analysis. γ,δ-Unsaturated β-keto esters (**5**) were produced in excellent yield where the ester consisted of a small alkyl group (Table 1, entries (**a**) and (**b**)), and in moderate yield when R^1 was derived from a bulky chiral alcohol (entries (**c**) and (**d**)).

The method of Pollet and Gelin[6] also produced the desired γ,δ-unsaturated β-keto ester, but this route was lower yielding and more involved (for example, compound (**5a**) was synthesised in 28 % yield from tiglyl chloride, ethyl hydrogen malonate and isopropyl magnesium bromide).

In the condensation step, standard Knoevenagel conditions[7] (catalytic piperidine, dichloromethane, RT)



(3) (4) (5) (6)

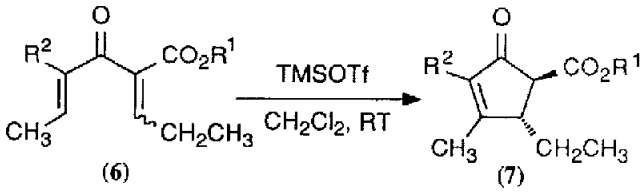
Scheme 2

Table 1. Synthesis of Dienone Esters (6)

	R^1	R^2	% yield of (5)	% yield of (6)
(a)	Et	Me	91	38
(b)	Et	H	100	40
(c)	(-)-menthyl	Me	31	59
(d)	(-)-menthyl	H	35	43

failed to produce the desired products using esters (**5a**) and (**5b**). Addition of 4Å molecular sieves to remove the water produced at the dehydration stage resulted in only low yields of (**6a**) and (**6b**), which were also unacceptably contaminated with undesired side products. This methodology was abandoned in favour of Lehnert's conditions for Knoevenagel condensations between ketones and malonate esters using titanium tetrachloride and pyridine.[8] Reaction between various γ,δ-unsaturated β-keto esters (**5**) and propionaldehyde afforded the 2-alkylidine derivatised targets (**6**) in a much cleaner reaction (Scheme 2 and Table 1).

Nazarov cyclisation of the α,α'-dienone esters (**6**) obtained was effected using trimethylsilyltriflate at room temperature (Scheme 3 and Table 2), which was found to be an effective alternative to both trimethylsilyliodide and other Lewis acids.[3e]



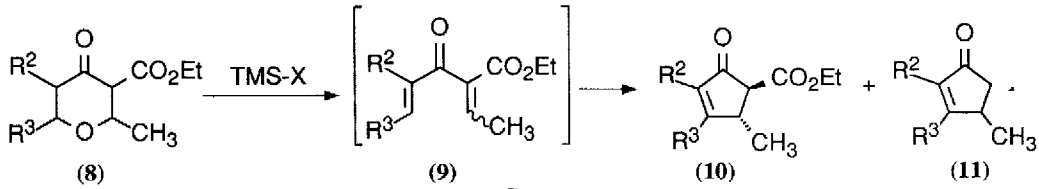
(6) (7)

Scheme 3

Table 2.

	R^1	R^2	% yield of (7)
(a)	Et	Me	31
(b)	Et	H	0
(c)	(-)-menthyl	Me	39
(d)	(-)-menthyl	H	0

Trimethylsilyltriflate was also found to effect Nazarov-type cyclisation of 3-ethoxycarbonyl tetrahydro-γ-pyrones of type (**8**) (Scheme 4). This type of transformation has previously been described by Takeda *et al.*[3f] using ten equivalents trimethylsilylchloride-sodium iodide in dimethylformamide at 120 °C, in order to effect initial ring opening of species (**8**) and subsequent Nazarov cyclisation of the presumed intermediate α,α'-dienone ester (**9**). In our hands these conditions gave not only the desired cyclopentenone ester (**10**), but also the product of dealkoxycarbonylation (**11**) (Table 3). The formation of these by-products (**11**) is not surprising in view of the well-known precedent for ester cleavage by trimethylsilyliodide.[9]



Scheme 4.

Table 3. Nazarov Cyclisations of Tetrahydropyrones

			TMSCl-NaI/DMF/120 °C %yields:		TMSOTf/CH_2Cl_2/RT %yields:	
(8)	R^2	R^3	**(10)**	**(11)**	**(10)**	**(11)**
(a)	Me	Me	46	23	55	0
(b)	$-(CH_2)_4-$		37	37	77	0

This Nazarov-type cyclisation was found to proceed in good yield in the presence of five equivalents of trimethylsilyltriflate in dichloromethane *at room temperature* (Table 3). None of the product of dealkoxycarbonylation (**11**) was detected, and the reaction proceeded under much milder conditions than previously employed. The cyclisations of both dienones and tetrahydropyrones were completely diastereoselective for the *trans*[10] isomers of (**7**) and (**10**), presumably as a result of facile epimerisation of the ester group.

Takeda[3f] and others[2,3e] have experienced difficulty in the cyclisation of α,α'-dienones or tetrahydro-γ-pyrones where R^2=H, and trimethylsilyltriflate similarly failed to induce cyclisation of such species (e.g. Table 2, entries (**b**) and (**d**)).

In conclusion, we have shown the use of trimethylsilyltriflate in dichloromethane at room temperature to be an effective and mild reagent for the Nazarov-type cyclisation of both dienone- and tetrahydro--γ-pyrone-esters. The required dienone esters were synthesised by a short two-step acylation-Knoevenagel sequence.

The following are representative experimental procedures for the steps described.[11]

Ethyl-4-methyl-3-oxo-hex-4-enoate (5a).

Ethyl acetate (AR grade, 2.2 ml, 22.7 mmol, 1 eq) was added dropwise to LDA (2 eq) in THF (15 ml) at -78 °C under argon over a period of five minutes; the reaction mixture was left to stir for a further twenty minutes and tiglyl chloride (freshly distilled, 2.69 g, 22.7 mmol, 1 eq) was added in a dropwise manner over fifteen minutes. Stirring was continued at -70 °C for a further two hours whereupon the reaction mixture was quenched with 20 % aqueous hydrochloric acid (25 ml) and then allowed to warm to room temperature. The layers were separated and the aqueous phase extracted twice with ether; the combined organic phases were dried over anhydrous magnesium sulphate and concentrated *in vacuo* to yield a mobile yellow *oil* (3.502 g, 91%) which was almost pure by t.l.c.. Further purification could be achieved by flash chromatography or Kugelrohr distillation as desired.

General Method for the Titanium Tetrachloride-Pyridine Mediated Knoevenagel Condensation of γ,δ-Unsaturated β-Keto Esters (5) with Propionaldehyde.

An oven-dried 25 ml flask was purged with argon, cooled to 0 °C and charged with THF (5.8 ml), carbon tetrachloride (0.72 ml) and titanium tetrachloride (0.315 ml, 2.9 mmol, 2 eq.). To the resulting bright yellow suspension was added the γ,δ-unsaturated β-keto ester (**5**) (1.45 mmol, 1 eq) in THF (1.5 ml) followed by propionaldehyde (0.1 ml, 1.45 mmol, 1 eq); finally a solution of dry pyridine (0.464 ml, 5.74 mmol, 4 eq)

in THF (1 ml) was added over 10-15 minutes. The reaction mixture was left to stir overnight, allowing to warm gradually to room temperature. The reaction was quenched with water, extracted three times with ether and washed with saturated sodium bicarbonate solution and saturated brine. The combined ether extracts were then dried over anhydrous magnesium sulphate, concentrated *in vacuo* and kugelrohr distilled at reduced pressure. The α,α'-dienones **(6)** were produced as mobile pale yellow oils. T.l.c. analysis (ethyl acetate:hexane; 20:80) showed the product to be virtually uncontaminated with starting material and the material was used directly for the subsequent Nazarov cyclisation.

Conditions for Trimethylsilyltriflate-Induced Nazarov Cyclisation of α,α'-Dienone Esters (6) and Tetrahydropyrones (8).

To a stirred solution of the α,α'-dienone ester **(6)** or the tetrahydropyrone **(8)** (0.47 mmol) in dry dichloromethane (2 ml) under argon at room temperature was added trimethylsilyltriflate (1.41 mmol, 3 eq for the dienones; 2.35 mmol, 5 eq for the tetrahydropyrones). The reaction mixture was stirred at room temperature for 2 hours and then diluted with water and dichloromethane. After separation of the organic phase, the aqueous layer was extracted with dichloromethane and the combined organic phases dried over anhydrous magnesium sulphate and concentrated *in vacuo*. The resulting yellow oil was purified by flash chromatography or MPLC (ethyl acetate:hexane, 25:75) to yield the desired cyclopentenone **(7)** or **(10)**.

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REFERENCES AND NOTES.

1. Present address: Department of Chemistry, University of Manchester, Oxford Road, Manchester, M13 9PL, UK.
2. Santelli-Rouvier, C.; Santelli, M. *Synthesis*, **1983**, 429-442.
3. (a) Denmark S.E.; Jones T.K. *J. Am. Chem. Soc.*, **1982**, *104*, 2642-2645; *Helv. Chim. Acta*, **1983**, *66*, 2377-2396; *ibid.*, **1983**, *66*, 2397-2411; Denmark S.E.; Habermas K.L.; Hite G.A.; Jones, T.K. *Tetrahedron*, **1983**, *42*, 2821-2829; Denmark S.E.; Habermas K.L.; Hite G.A. *Helv. Chim. Acta*, **1988**, *71*, 168-194; Denmark S.E.; Hite G.A. *ibid.*, **1988**, *71*, 195-208; Denmark S.E.; Klix, R.C. *Tetrahedron*, **1988**, *44*, 4043-4060; (b) Cooke, F.; Schwindeman J.; Magnus, P. *Tetrahedron Lett.*, **1979**, 1995-1998; (c) Fristad, W.E.; Dime, D.S.; Bailey T.R.; Paquette, L.A. *Tetrahedron Lett.*, **1979**, 1999-2002; (d) Paquette, L.A.; Fristad, W.E.; Dime D.S.; Bailey, T.R. *J. Org. Chem.*, **1980**, *45*, 3017-3028; (e) Marino J.P.; Linderman, R.J. *J. Org. Chem.*, **1981**, *46*, 3696-3702; (f) Sakai, T.; Miyata K.; Takeda, A. *Chem. Lett.*, **1985**, 1137-1138; (g) Peel M.R.; Johnson, C.R. *Tetrahedron Lett.*, **1986**, *27*, 5947-5950.
4. Oppolzer, W. *Tetrahedron*, **1987**, *43*, 1969-2004.
5. Rathke M.W.; Deitch, J. *Tetrahedron Lett.*, **1971**, 2953-2956.
6. Pollet P.; Gelin, S. *Synthesis*, **1978**, 142-143.
7. Jones, G. *Organic Reactions*, **1967**, *15*, 204-599.
8. Lehnert, W. *Tetrahedron*, **1973**, *29*, 635-638.
9. Olah, G.A.; Narang, S.C.; Gupta, B.G.B.; Malhotra, R. *J. Org. Chem.*, **1979**, *44*, 1247-1251.
10. $J_{vic.}$ = 2.75 Hz. Modelling studies using Macromodel (W.C. Still, Columbia University, New York), and literature precedent[12] suggest a *trans*-arrangement.
11. Satisfactory i.r., n.m.r. (^{1}H and ^{13}C), and mass spectra, and elemental analysis and/or accurate mass were obtained for all new compounds. All yields are unoptimised.
12. Isobe, K.; Fuse, M.; Kosugi, H.; Hagiwara, H.; Uda, H. *Chem Lett.*, **1979**, 785-788; Danielli, R.; Martelli, G.; Spunta, G.; Rossini, S.; Cainelli, G.; Panunzio, M. *J. Org. Chem.*, **1983**, *48*, 123-125; Shoppee, C.W.; Cooke, B.J.A. *J. Chem. Soc., Perkin Trans. 1*, **1973**, 1026-1030.

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