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CONJUGATE ADDITIONS ON α-PHENYLTHIO-α,β-UNSATURATED OXAZOLINES. NOVEL SYNTHESIS OF 3,4-DISUBSTITUTED COUMARINS.

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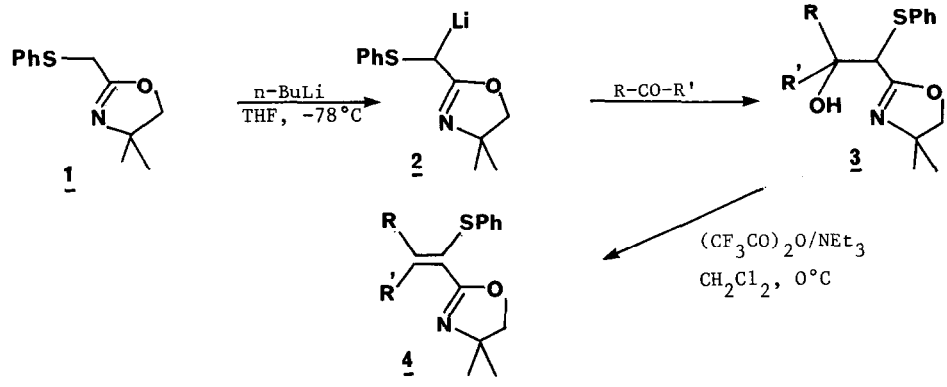
Summary : Nucleophilic addition of organolithium, Grignard and hydride reagents to α-phenylthio-α,β-unsaturated oxazolines is regioselective and occurs in a 1,4-fashion. This leads to a novel, versatile synthesis of polysubstituted coumarins.

Olefins geminally substituted by both an electron withdrawing and a thioether groups are versatile Michael acceptors. Interest in these alkenes stems from their increased reactivity (compared to non-heteroatom-substituted counterparts) and from the potential elaboration of the adducts due to the rich chemistry of the sulfide group. Until now, only mild carbon nucleophiles (enolates, organocopper reagents)[1] have been reported to add in a conjugate manner to α-thio unsaturated esters. We describe now the regioselective condensation of strong nucleophiles in a 1,4-fashion when the carboxyl group is protected as an oxazoline[2,3].

Preparation of the requisite α-phenythio conjugated oxazolines 4 was readily carried out. Thus, 5,5-dimethyl 2-phenylthiomethyl oxazoline 1 reacted via its lithioazaenolate 2 [4] to generate the alcohols 3, dehydration of which under appropriate conditions [trifluoroacetic anhydride (1.2 eq), triethylamine (2 eq), 4,4-dimethylaminopyridine (0.05 eq)] led to the olefins 4 with satisfactory overall yields (table I). β-Aryl substituted derivatives 4c,d were also prepared through a Knoevenagel reaction under phase transfer conditions [50% aqueous NaOH (1 eq), Aliquat 336 (0.05 eq)]. In both procedures, the formation of the trisubstituted alkenes (R' = H) from the aldehyde precursor is stereoselective with an Z:E ratio higher than 90:10 [5].



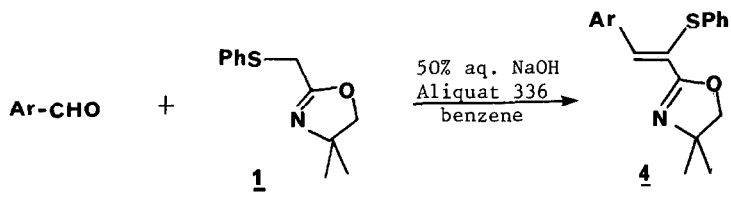
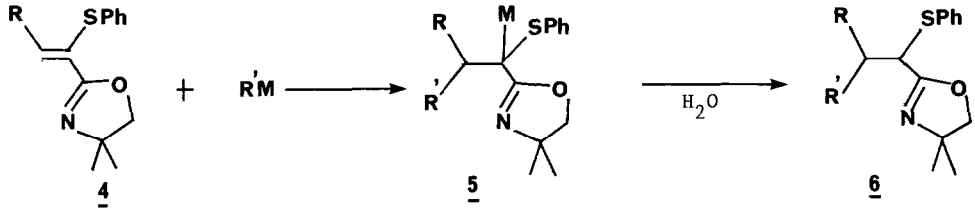


Table I

	R	R'	4, yield (%) [6]	Mp or Bp (°C/mmHg)
a	H	H	68	64
b	CH_3	H	87	39, 107(10^{-1})
c	C_6H_5	H	88 (86*)	38
d	o $CH_3O-CH_2O-C_6H_4$	H	86 (94*)	88
e	CH_3	CH_3	92	115(10^{-1})
f	$-(CH_2)_4-$		77	73

* Reactions carried out under phase transfer conditions.

The addition of aliphatic, aromatic or acetylenic organolithium derivatives to a cold solution (-78°C) of the substrates 4 immediately gave the dark yellow color of the azaenolates 5 , the subsequent hydrolysis of which yielded the expected β-disubstituted oxazolines 6. We have previously reported[4] the alkylation of lithio reagent intermediates 5 (prepared by an alternative route), allowing in this case the formation of a second carbon-carbon bond in a single step. Treatment of the conjuguated oxazolines 4 with a solution of a Grignard reagent under the conditions described for the organolithium reagents resulted in a low yield of 1,4-addition (< 5%) ; however, after several hours at 0°C the condensation proceeded affording the adducts 6 in reasonable yields (see table II, entries 3 and 7).



Reaction conditions : M = Li R'M (1.05 eq), Et_2O, -78°C, 1 h
M = MgX R'M (1.1 eq), THF, 0°C, 3 h

Table II

	R	R'M	6, yield (%) [7]	Bp (°C/mmHg)
1	CH_3	CH_3Li	84	85(10^{-2})
2	CH_3	n-C_4H_9Li	91	175(10^{-1})
3	CH_3	n-C_4H_9MgBr	82	"
4	CH_3	n-$C_4H_9C{\equiv}CLi$	76	210(10^{-1})
5	CH_3	C_6H_5Li	86	200(10^{-1})
6	C_6H_5	CH_3Li	81	"
7	C_6H_5	CH_3MgI	79	"
8	C_6H_5	n-C_4H_9Li	90	240(10^{-1})

The addition of various hydrides to the unsaturated oxazolines 4 also occured regioselectively at the terminal position of the conjugated moiety ; sodium cyanoborohydride (MeOH-AcOH, 0°C) proved to be the reagent of choice[8], the reduction of 4b,c quantitatively affording the saturated oxazolines 6 (R' = H).

These efficient Michael additions were subsequently applied to a synthesis of coumarins. Although numerous methods of preparation of these heterocycles have been reported, they have generally required rather harsh conditions (strongly acidic media and/or high temperature)[9].

In our approach, the pivotal intermediates 8 could be generated via two complementary pathways. In the first one (path A) the organolithiun reagent 7, directly accessible from phenol methoxymethylether[10] was added to the alkenes 4, then alkylated or hydrolyzed. In the second procedure (path B), the easily prepared 4d (table I) is condensed with an organometallic reagent or a reducing agent, then quenched as previously described. Further elaboration of oxazolines 8 into the coumarins 10 proceeded through a mild acidic hydrolysis (4 N HCl in refluxing THF) to produce the lactones 9, followed by a dehydrosulfenylation (1 eq MCPBA, then refluxing in carbon tetrachloride) to yield the desired coumarins in fair overall yields (table III).

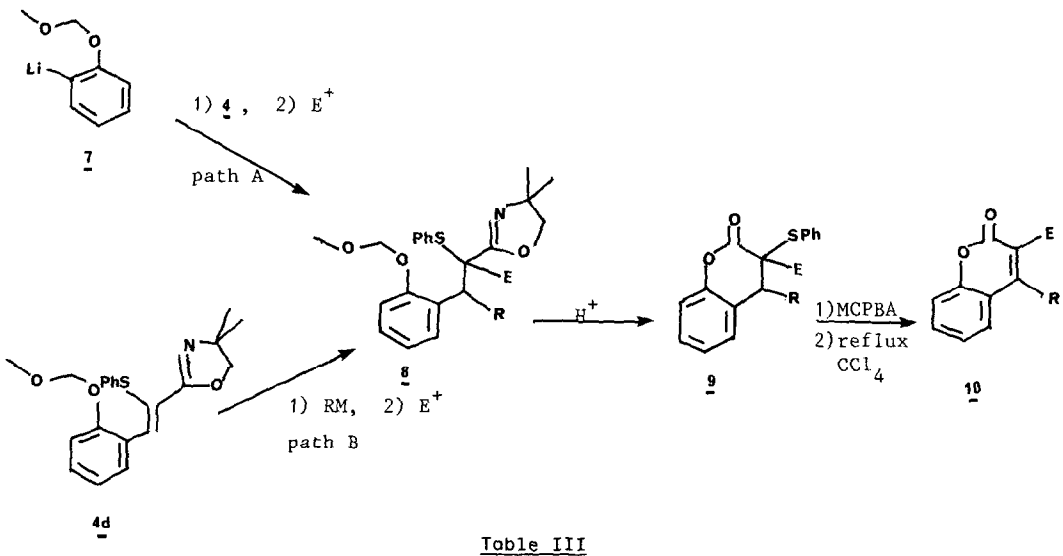
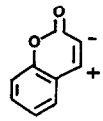


Table III

Path	R	E	8, yield (%) [7]	10, yield (%) [7]	Mp (°C)
A	CH_3	H	89	68	82 [11]
A	C_6H_5	CH_3 [a]	83	77	79 [12]
B	C_2H_5 [b]	H	76	-	
B	n-C_4H_9 [c]	H	92	-	
B	H	CH_3 [d]	89	62	90 [11]

a) 2 eq of methyl iodide were used as a quench. b) from EtMgBr (1.1 eq). c) from n-BuLi (1.05 eq). d) overall yield from 4d through a sequence of reduction ($NaBH_3CN$, quant.), alkylation (n-BuLi, MeI).

By this method, the R substituent located at the 4 position of the coumarin ring could be introduced either as an aldehyde (path A) or an organometallic reagent (path B). In this latter case, the oxazoline 4d is formally equivalent to the synthon :



As ring substituted derivatives of the organolithium reagent 7 are known[13], their use in this Michael reaction and the subsequent condensation of the resulting azaenolates with various electrophiles[14] should broaden the scope of this methodology for the preparation of highly substituted coumarins.

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5) Determined by ^{1}H NMR spectroscopy. The lower field resonance for the vinylic proton of the major isomer is indicative of a Z configuration, see : Pascual,C. ; Meier,J. and Simon,W. *Helv.Chim.Acta*, **1966**, 49, 164.
6) Overall yields from 1 of pure isolated compounds after distillation or recrystallisation (hexane, -20°C).
7) Yield after flash chromatography [chloroform-ethyl acetate (100:5)] followed by rectification in a Kugelrohr. Analytical and spectroscopic data (^{1}H NMR, MS, IR) are in good agreement with the proposed structures.
8) 6b (R=Ph, R'=H) was obtained in 85% yield using diisobutylaluminum hydride in hexane (20°C, 15 h) and in 80% yield with $NaBH_4$ in ethanol. In this latter case, the reaction is slow (48 h) and requires a large excess (20 eq) of the reducing agent.
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