Pergamon

Tetrahedron Letters 40 (1999) 3741–3744

TETRAHEDRON LETTERS

2,6-Diphenyl-4*H*-chalcogenopyran-4-ones and 2,6-diphenyl-4*H*-chalcogenopyran-4-thiones: a new catalyst for the Baylis-Hillman reaction

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Received 19 February 1999; revised 10 March 1999; accepted 12 March 1999

Abstract

2,6-Diphenyl-4*H*-chalcogenopyran-4-ones and 2,6-diphenyl-4*H*-chalcogenopyran-4-thiones, a new series of catalysts for the Baylis-Hillman reaction, were investigated. The reactions proceeded smoothly in the presence of 1 mol eq. of $TiCl_4$ under atmospheric pressure at 0°C, giving adducts in moderate to high yields. Chalcogenopyranones and chalcogenopyranthiones were a more efficient kind of catalyst than Me_2S.

Keywords: Baylis-Hillman reactions; Thiopyrans; Thiopyrylium ions; Titanium and compounds

The Baylis-Hillman reaction catalyzed by a tertiary amine or a phosphine is a carbon-carbon bond forming reaction between aldehydes and activated alkenes which serves as versatile building blocks for organic synthesis [1-3]. The drawback to this methodology is its slow reaction rate, and many research groups have examined a variety of methods to accelerate the reaction including an asymmetric reaction [4-14]. Recently, we have investigated the chalcogeno-Baylis-Hillman reaction catalyzed by a chalcogenide in the presence of a Lewis acid [15-17]. The reaction proceeded smoothly under atmospheric pressure at room temperature. We have developed an asymmetric version of the chalcogeno-Baylis-Hillman reaction by the use of a hydroxy chalcogenide [18]. Alkylation of 4*H*-chalcogenopyran-4-ones took place not at the chalcogen atom but at the oxygen atom because of formation of stable chalcogenopyrylium salts [19-21]. This prompted us to develop a new series of catalysts, namely, 4*H*-chalcogenopyran-4-chalcogenones (Scheme 1). We will report on 2,6-diphenyl-4*H*-chalcogenopyran-4-ones and 2,6-diphenyl-4*H*-chalcogenopyran-4-thiones **1-4** [22,23] as a novel kind of catalysts for the Baylis-Hillman reaction.

p-Nitrobenzaldehyde and 2 mol eq. of methyl vinyl ketone were treated with a catalytic amount of 2,6-diphenyl-4*H*-chalcogenopyran-4-ones and their thione derivatives **1-4** in the presence of 1 mol eq. of Lewis acids in CH_2Cl_2 at 0°C for 1 h under atmospheric pressure

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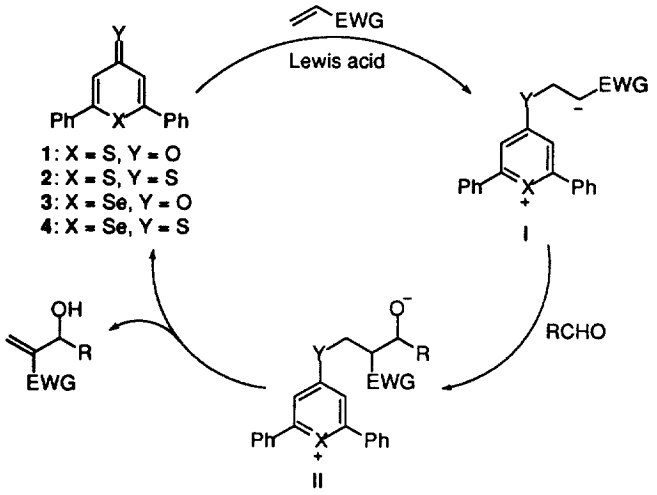
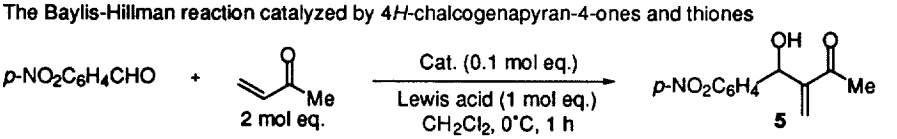
0040-4039/99/$ - see front matter
PII: S0040-4039(99)00585-7



Scheme 1

(Table 1). First, we examined some Lewis acids in reactions with 2,6-diphenyl-4*H*-thiopyran-4-one **1** as a catalyst (entries 1-4) and found that $TiCl_4$ gave the best result (entry 1). A reaction with **1** in the absence of $TiCl_4$ provided no coupling product. Next, other catalysts **2-4** and Me_2S were examined in the presence of 1 mol eq. of $TiCl_4$ (entries 5-8). All catalysts **1-4** gave better results than Me_2S. Moreover, all catalysts were recoverable without significant loss, although thiones **2** and **4** were partly transformed into ketones **1** and **3**, respectively, during the purification of the reaction mixtures by preparative TLC on silica gel.

Table 1
The Baylis-Hillman reaction catalyzed by 4*H*-chalcogenapyran-4-ones and thiones



Entry	Cat.	Lewis acid	5 (%Yield)[a]
1	1	$TiCl_4$	86
2	1	$SnCl_4$	No reaction
3	1	$AlCl_3$	70
4	1	$BF_3{\cdot}Et_2O$	No reaction
5	2	$TiCl_4$	98
6	3	$TiCl_4$	100
7	4	$TiCl_4$	96
8	Me_2S	$TiCl_4$	72

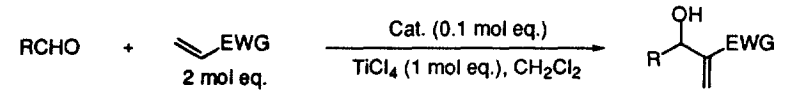
[a]Isolated yield based on *p*-nitrobenzaldehyde.

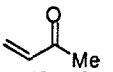
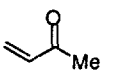
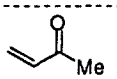
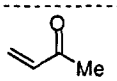
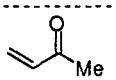
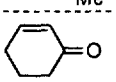
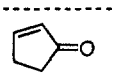
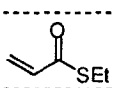
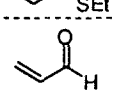
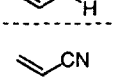
No intermediates such as **I** or **II**, shown in Scheme 1, could be isolated. It was suggested, however, that the reactions proceeded *via* **I** and **II** because 4*H*-chalcogenopyran-4-ones were *O*-alkylated at the carbonyl group rather than the chalcogen atom [19,20] even in the case of

4*H*-telluropyran-4-one [21].[1]

First, several aldehydes and methyl vinyl ketone were treated with 0.1 mol eq. of thiopyranthione **2** and selenopyranone **3** in the presence of 1 mol eq. of $TiCl_4$ in CH_2Cl_2 under atmospheric pressure (Table 2). Reactions of aromatic aldehydes gave adducts **6-8** in moderate to high yields even for 1 h at 0°C (entries 1-6). Treatment of aliphatic aldehydes

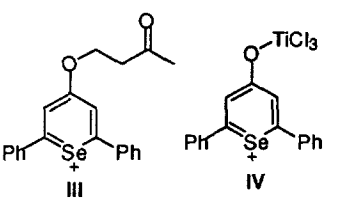
Table 2
The Baylis-Hillman reaction of some aldehydes and activated alkenes with thiopyranthione **2** and selenopyranone **3**



Entry	Cat.	Aldehyde	Alkene	Conditions	Product (%Yield)[a]
1	2	*p*-ClC_6H_4CHO		0°C, 1 h	**6** (95)
2	3			0°C, 1 h	**6** (86)
3	2	PhCHO		0°C, 1 h	**7** (45)
4	3			0°C, 1 h	**7** (80)
5	2	*p*-MeC_6H_4CHO		0°C, 1 h	**8** (32)
6	3			0°C, 1 h	**8** (43)
7	2	$PhCH_2CH_2CHO$		0°C, 1 h	**9** (73)
8	3			0°C, 1 h	**9** (86)
9	2	^iPrCHO		0°C, 1 h	**10** (44)
10	3			0°C, 1 h	**10** (46)
11	2	*p*-$NO_2C_6H_4CHO$		0°C, 1 h	**11** (80)
12	3			0°C, 1 h	**11** (81)
13	2	*p*-$NO_2C_6H_4CHO$		0°C, 1 h	**12** (70)
14	3			0°C, 1 h	**12** (75)
15[b]	2	*p*-$NO_2C_6H_4CHO$		r.t., 20 h	**13** (90)
16[b]	3			r.t., 20 h	**13** (84)
17	2	*p*-$NO_2C_6H_4CHO$		0°C, 1 h	**14** (58)
18	3			0°C, 1 h	**14** (70)
19	2	*p*-$NO_2C_6H_4CHO$		reflux, 24 h	**15** (32)
20	3			reflux, 24 h	**15** (53)

[a]Isolated yield based on an aldehyde. [b]The crude products were treated with DBU before purification [17].

1 This mechanism was suggested by ^1H NMR experiments. In the ^1H NMR spectrum of a mixture of selenopyranone **3**, 1 mol eq. of methyl vinyl ketone and 1 mol eq. of $TiCl_4$, two sets of signals derived from methyl vinyl ketone were observed; one was due to methyl vinyl ketone itself, and the other [δ 2.35 (3 H, s, Me), 3.03 and 3.76 (each 2 H, t, J = 6.4 Hz)] were assigned to a selenopyrylium structure **III**. On the other hand, only one set of signals derived from **3** was observed; these peaks were assigned to selenopyrylium salts **III** and **IV** and overlapped with each other. The signals were identical with those in the ^1H NMR spectrum of a mixture of **3** and $TiCl_4$ (1 mol eq.), which were assigned to **IV**. The 3-H signals of selenopyrylium salts **III** and **IV** were observed at δ 8.37, considerably lower than that of selenopyranone **3** at δ 7.30. Generally, 3-H signals of chalcogenopyrylium salts appear at about δ 8.5 [24], and the results support the formation of selenopyrylium intermediates **III**.



for 1 h at 0°C also provided adducts **9** and **10** in moderate to high yields (entries 7-10). In most cases, selenopyranone **3** gave better results than thiopyranthione **2**. Next, we examined the reactions of several activated alkenes and *p*-nitrobenzaldehyde with thiopyranthione **2** and selenopyranone **3** as a catalyst in the presence of 1 mol eq. of $TiCl_4$ in CH_2Cl_2 under atmospheric pressure. Adducts **11-15** were obtained in moderate to high yields from 2-cyclohexenone, 2-cyclopentenone, *S*-ethyl thioacrylate, acrolein and acrylonitrile (entries 11-20), whereas no coupling product was obtained in the case of methyl acrylate.

The general procedure for the chalcogenopyran-catalyzed Baylis-Hillman reaction is as follows: To a stirred solution of a chalcogenopyranone (0.05 mmol), *p*-nitrobenzaldehyde (75 mg, 0.5 mmol) and methyl vinyl ketone (105 mg, 1 mmol) in dry CH_2Cl_2 (1.5 cm^3) was added dropwise $TiCl_4$ (55 μdm^3, 0.5 mmol) at 0°C. The mixture was stirred at the same temperature for 1 h, and the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (2 cm^3). The inorganic precipitate was removed by filtration through Celite™, and the filtrate was dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by preparative TLC on silica gel eluted with CH_2Cl_2–acetone (20:1, v/v) to give adduct **5**.

In summary, we have developed a new series of catalysts, 4*H*-chalcogenopyran-4-chalcogenones, for the Baylis-Hillman reaction. A detailed mechanistic study including isolation of intermediates, and further exploration of the catalysts and their modification for application to asymmetric reaction are now in progress.

Acknowledgments This work was supported in part by a Grant-in-Aid for Scientific Research on Priority Areas (A), "The Chemistry of Inter-element Linkage" (No. 09239241 and 10133244) from the Ministry of Education, Science, Sports, and Culture, Japan.

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