



Titanocene(II)-promoted desulfurizative acylation of thioacetals with alkanenitriles

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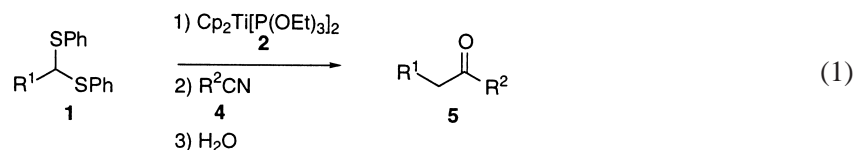
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Abstract

Ketones were obtained in good yields by titanocene(II)-promoted reaction of thioacetals with alkanenitriles. The regioselective formation of α -substituted ketone was observed when the reaction was carried out in the presence of methyl iodide or benzyl bromide. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: acylation; alkylation; thioacetal; titanium; titanium compounds.

Recently, the chemistry of carbene complexes of transition metals has been extensively studied and a number of useful synthetic reactions have been developed.¹ A methylenide complex of titanium formed from Tebbe reagent,² Grubbs reagent,³ or dimethyltitanocene⁴ is a synthetically useful metal carbene and is reactive toward carbon–carbon and carbon–heteroatom multiple bonds. Its reaction with alkanenitrile was first reported by Eisch and Piotrowski.⁵ They obtained acetophenone by the reaction of methylenidetitanocene with benzonitrile. Doxsee and his co-workers investigated the reactions of intermediary vinylimido complexes of titanium and reported the formal [4+2] cycloadditions with ketones, nitriles, and imines.⁶ Recently, we found that the desulfurization of thioacetals **1** with a low-valent titanium reagent $\text{Cp}_2\text{Ti}[\text{P}(\text{OEt})_3]_2$ **2** gave an organotitanium species which reacted with organic molecules having a multiple bond.⁷ These results suggest that the active species formed from thioacetals are alkylidenetitanocenes **3**. We then investigated the reaction of these organotitanium species with alkanenitriles **4** (Eq. 1).



Thioacetals **1** were treated with the low-valent titanium reagent **2** at room temperature for 15 min. The reaction of the resulting organotitanium compounds with alkanenitriles **4** for 1–3 h and the following hydrolysis produced the corresponding ketones **5** (Table 1). It is well known that the preparation

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Table 1
Desulfurizative acylation of thioacetals **1** with alkanenitriles **4**^a

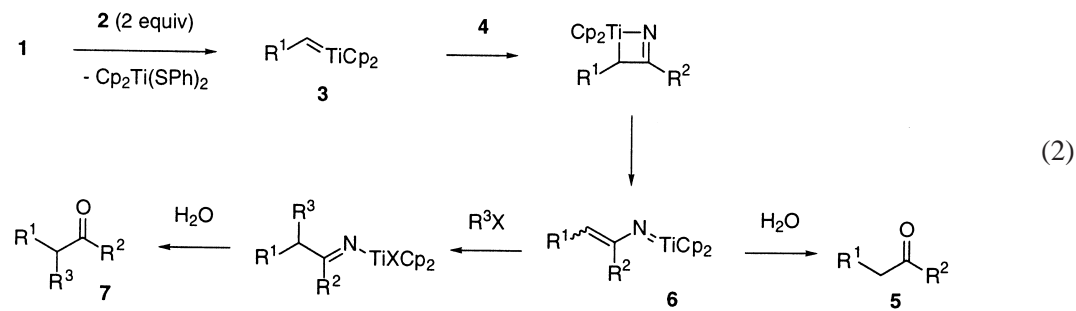
Entry	Thioacetal 1	Alkanenitrile 4	Time (h)	Product 5	Yield (%)	
1		1a Ph-CH ₂ -CH ₂ -CH ₂ -CN 4a	1		5a 60	
2	1a		4b	1.5		5b 66
3	1a		4c	3		5c 63
4		1b CH ₃ -CH ₂ -CH ₂ -CN 4d	1.5	5a	68	
5	1b		4e	1		5d 66
6	1b		4f	1		5e 85
7		1c Ph-C(CH ₃) ₂ -CN 4g	3		5f 65	
8		1d 4d	1		5g 60	
9		1e 4a	1.5		5h 65	
10		1f 4d	1		5i 58	

a) All the reactions were performed by a similar procedure as described in the text, unless otherwise noted.

of ketones by addition of organometallic compounds such as Grignard reagents to alkanenitriles is often affected by steric hindrance, and the yields are generally low in the case of α,α -disubstituted alkanenitriles.⁸ The most remarkable feature of the present acylation is the generality in the choice of substrates. As shown in Table 1, ketones were obtained in good yields even when the sterically hindered alkanenitriles were employed.

The following is a typical experimental procedure. Finely powdered molecular sieves 4 A (180 mg), magnesium turnings (53 mg, 2.2 mmol; purchased from Nacalai Tesque Inc., Kyoto, Japan) and Cp_2TiCl_2 (448 mg, 1.8 mmol) were placed in a flask and dried by heating with a heat gun under reduced pressure

(2–3 mmHg). During this procedure, care is taken not to sublime Cp_2TiCl_2 . After cooling, THF (4 ml) and $\text{P}(\text{OEt})_3$ (0.61 ml, 3.6 mmol) were added successively with stirring at room temperature under argon. After 3 h, a THF (1 ml) solution of 3-phenyl-1,1-bis(phenylthio)propane (**1b**) (202 mg, 0.6 mmol) was added and the reaction mixture was stirred for 15 min. Valeronitrile (**4d**) (42 mg, 0.5 mmol) in THF (1.5 ml) was added and the mixture was stirred for a further 1.5 h. The reaction was quenched by addition of 1 M NaOH and the insoluble materials were filtered off through Celite. The filtrate was extracted with ether and the organic phase was dried over Na_2SO_4 . After removal of the solvent, the residue was purified by PTLC (hexane:AcOEt 9:1) to yield 69 mg (68%) of 1-phenyloctan-4-one (**5a**).



We tentatively propose that this reaction proceeds via the formation of vinylimido complex **6** similarly to the reaction of methylidenetitanocene (Eq. 2). Unlike the unsubstituted vinylimido complex ($\text{R}^1=\text{H}$), however, the intermediate of the present reaction showed no reactivity toward carbonyl compounds, nitrile, and imine. We further investigated its reaction with electrophiles and found that alkylation proceeded to give the monoalkylated ketones **7** on treatment with reactive alkyl halides such as methyl iodide or benzyl bromide (Table 2).⁹ This acylation–alkylation sequence was successfully applied to the preparation of cyclic ketones; α -substituted cyclohexanones **7e** and **h** were obtained by the reaction using 5-halovaleronitrile (entries 5 and 8).

In summary, we have developed a new method for the preparation of ketones from thioacetals and alkanenitriles. Further study on the reaction of the organotitanium intermediates is currently under way.

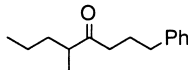
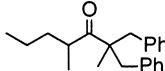
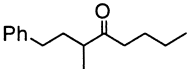
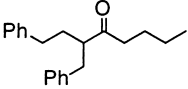
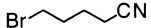
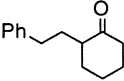
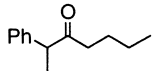
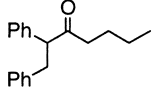
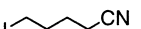

Acknowledgements

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Table 2
Desulfurizative acylation–alkylation of thioacetals **1**^a

Entry	Thioacetal 1	Alkanenitrile 4	Alkyl Halide (equiv)	Time (h)	Products (Yield / %) ^b
1	1a	4a	MeI (1.2)	1.5	 7a (66) 5a (7)
2	1a	4c	MeI (3.6)	3	 7b (46) 5c (28)
3	1b	4d	MeI (1.2)	1.5	 7c (74) 5a (7)
4	1b	4d	PhCH ₂ Br (3.6)	1.5	 7d (40) 5a (12)
5 ^c	1b	 4h	-	2	 7e (43)
6	1d	4d	MeI (1.2)	1.5	 7f (62)
7	1d	4d	PhCH ₂ Br (3.6)	1.5	 7g (52) 5g (18)
8 ^c	1d	 4i	-	2	 7h (58)

a) A mixture of alkanenitrile **4** and alkyl halide was added after the reaction of thioacetal **1** with the low-valent titanium species **2**.

b) Isolated yield. c) Carried out using Cp₂TiCl₂ (4.2 equiv), magnesium turnings (4.2 equiv), P(OEt)₃ (8.4 equiv), and molecular sieves (100 mg / 1 mmol of Cp₂TiCl₂).

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9. When the reaction of **1b** with **4d** was carried out in the presence of ethyl iodide (3.6 equiv.), the alkylated ketone, 3-ethyl-1-phenyloctan-4-one, was obtained in 18% yield along with **5a** (46%). However, a similar reaction using butyl iodide produced no alkylation product.