The Heteroatomic Chains and Their Derived Cyclic Products XI.[1] A Synthesis of 2-(Dialkylhydrazono)thioacetophenones as Agents in the Preparation of 3,4-Dihydro-2*H*-1,4-thiazines and 2*H*-1,4-Thiazines

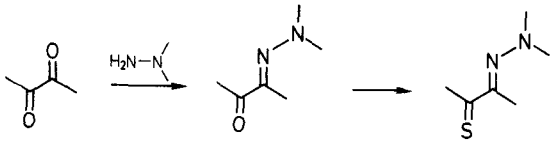
Alain Reliquet, Rafaa Besbes, Françoise Reliquet, Jean Claude Meslin*
U.A. CNRS 475, 2, Rue de la Houssinière, F-44072 Nantes Cedex, France

We describe the preparation of 2-(dialkylhydrazono)-thioacetophenones starting from their oxygenated analogs. These compounds are used as building blocks in heterocyclic chemistry and lead to 3,4-dihydro-2*H*-1,4-thiazines or 2*H*-1,4-thiazines.

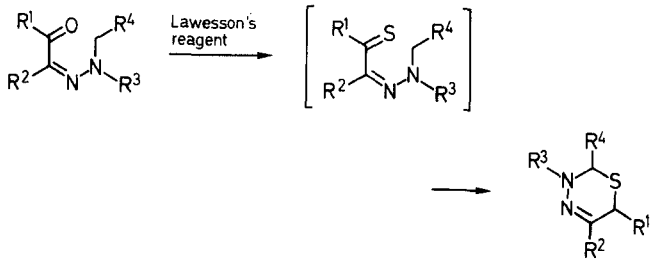
Since several years we are studying various heteroatomic chains containing sulfur and nitrogen. At first we studied the thioamide vinylogs[2] (3-aminopropenethiones -CS-CH=CH-NR_2). These compounds revealed interesting properties especially with regards to heterocyclic synthesis. We were able, for instance, to transform these vinylogs into new orginal thiophenes and thiopyrans.[3] Therefore we have studied the *N'*-thioacylformamidines[4] (-CS-N=CH-NR_2). It is quite evident that the structure of these products is derived from the thioamide vinylogs one if the methine group located in α-position of the thiocarbonyl is replaced by a nitrogen atom. On one hand these synthons allowed us to carry out original synthesis of thiazoles and 6*H*-1,3-thiazines.[5,6] On the other hand the latter were used recently in the development of an original strategy to prepare cephems and cephalosporins.[7,8]

The aim of this paper is to describe the synthesis of new heteroatomic chains whose structure would derive from the thioamide vinylogs one with the methine near the amino group substituted by a nitrogen atom. The study of these β-(hydrazono) thioketones (-CS-CH=N-NR_2) should then lead to new sulfur and nitrogen heterocyclic compounds according to an original method.

We tried to synthesize these compounds according to the preparation of the monohydrazone of a α-dicarbonyl compound followed by the thionation of the remaining carbonyl group.

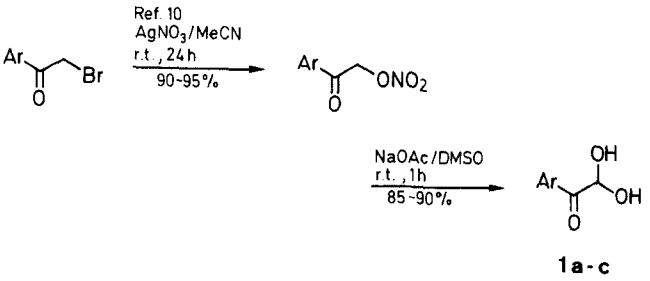


From our knowledge, no compound of this type has been described. Very recently, japanese workers[9] reported the synthesis of 3,6-dihydro-2*H*-1,3,4-thiadiazines starting from 3-dialkylhydrazono-2-alkanones in the presence of Lawesson's reagent.



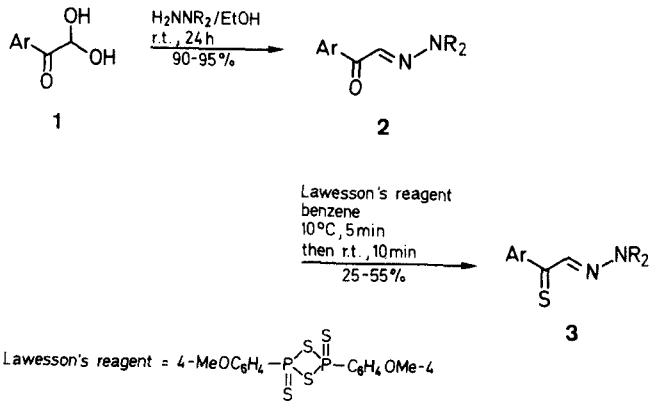
They seem to imply a possible route via β-(hydrazono) thioketones but these expected intermediates were neither isolated nor observed. Much harsher reaction conditions than those undermentioned probably make clear the difference between the results.

The work we describe starts from arylglyoxal hydrates **1**. Products **1b** and **1c** (which are not available) are prepared from the corresponding bromoacetophenones according to the method described by Kornblum.[10]



1	a	b	c
Ar	Ph	4-BrC_6H_4	4-ClC_6H_4

Therefore the monohydrazones **2** are synthesized by means of the action of 1,1-dimethylhydrazine or of 1-aminopiperidine starting from compounds **1**. The transformation of the carbonyl group of compounds **2** into thiocarbonyl is carried out using Lawesson's reagent.



2, 3	Ar	NR_2
a	Ph	NMe_2
b	Ph	*piperidino*
c	4-BrC_6H_4	NMe_2
d	4-ClC_6H_4	NMe_2

Compounds **3** are unstable; their synthesis must be carried out quickly. Yet, these compounds may be puri-

Table 1. 2-(Dialkylhydrazono)acetophenones **2** and 2-(Dialkylhydrazono)thioacetophenones **3** Prepared

Product	Yield (%)[a]	R_f[b]	^{1}H-NMR ($CDCl_3$/TMS)[c] δ, J (Hz)	MS *m/z*
2a	92	0.47	3.18 (s, 6H), 7.06 (s, 1H), 7.46 (m, 3H), 7.95 (m, 2H)	176 (M^+), 105 (C_6H_5CO)
3a	50	0.34	3.15 (s, 6H), 7.35 (m, 3H), 7.68 (m, 2H), 7.80 (s, 1H)	192 (M^+), 121 (C_6H_5CS)
2b	90	0.51	1.69 (m, 6H), 3.40 (m, 4H), 7.31 (s, 1H), 7.45 (m, 3H), 8.00 (m, 2H)	216 (M^+), 105 (C_6H_5CO)
3b	25	0.60	1.65 (m, 6H), 3.03, 3.43 (2m, 4H), 7.35 (m, 3H), 7.75 (m, 2H), 8.10 (s, 1H)	232 (M^+), 121 (C_6H_5CS)
2c	95	0.50	3.17 (s, 6H), 6.96 (s, 1H), 7.53, 7.84 (2d, 4H, ΣJ = 8.5)	254(M^+),[d] 183 (BrC_6H_4CO)
3c	51	0.26	3.20 (s, 6H), 7.48, 7.60 (2d, 4H, ΣJ = 8.5), 7.80 (s, 1H)	270(M^+),[d] 199 (BrC_6H_4CS)
2d	91	0.38	3.20 (s, 6H), 6.98 (s, 1H), 7.37, 7.93 (2d, 4H, ΣJ = 8.5)	210(M^+),[d] 139 (ClC_6H_4CO)
3d	55	0.33	3.15 (s, 6H), 7.28, 7.64 (2d, 4H, ΣJ = 8.5), 7.78 (s, 1H)	226(M^+),[d] 155 (ClC_6H_4CS)

[a] Purity of compounds is controlled by TLC.
[b] On plates silica gel MERCK 60 F_{254} compounds **2** CH_2Cl_2/EtOAc (90 : 10), compounds **3** petroleum ether (bp 55–60 °C)/EtOAc (80 : 20).
[c] Recorded at 90 MHz on a JEOL FX 90 Q.
[d] M^+ refers to ^{79}Br or ^{35}Cl.

fied by column chromatography and we were able to obtain the ^{1}H-NMR and MS spectra, however, was not possible to obtain elementary analysis. Further reactions with these products must be run quickly as well. The data of compounds **2** and **3** are collected in Table 1.

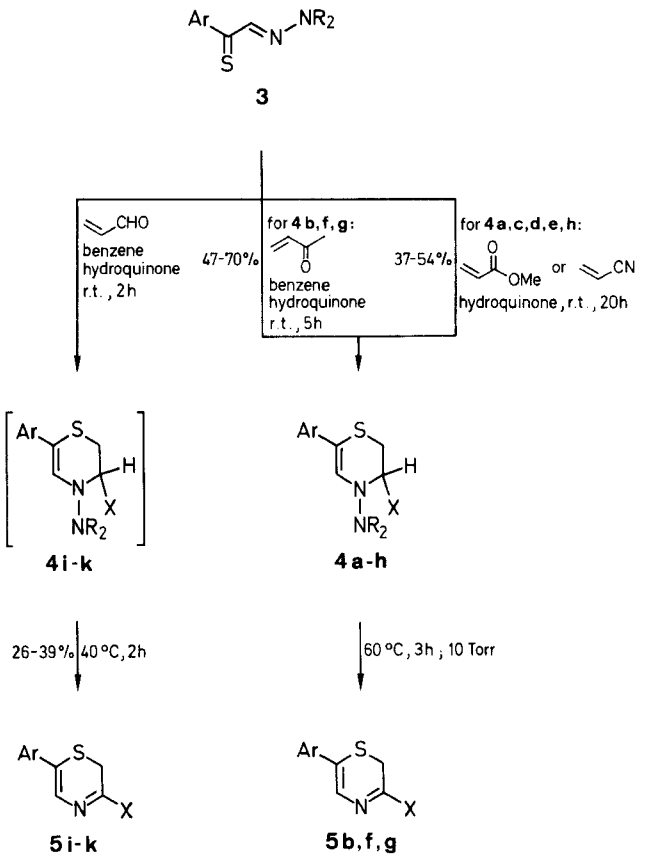
The configuration of compounds **3** has not been determinated but the ^{1}H-NMR spectra show only one isomer.

Thus, these new heteroatomic chains are used as heterodienes in Diels–Alder cycloaddition reactions with acrylic dienophiles. In this kind of reactions the *N'*-thioacylformamidines allowed us to place sulfur and nitrogen atoms in a relative position 1,3. Now, the (hydrazono) thioketones **3** led us to 3,4-dihydro-2*H*-1,4-thiazines **4** or to 2*H*-1,4-thiazines **5** after elimination of an amine molecule.

The evolution from **4** to **5** is not systematic and depends on the dienophile used. With an efficient electron-withdrawing group (X = CHO) intermediate compounds **4i–k** are not isolated. The dihydrothiazine can be identified after reaction with methyl vinyl ketone (X = COMe). It is then easy to convert it into the corresponding 2*H*-1,4-thiazine by heating under reduced pressure. Conversely, using methyl acrylate or acrylonitrile (X = CO_2Me, CN), the hydrogen bound at carbon 3 of compounds **4** obtained is not acidic enough and the removal of amine is not observed.

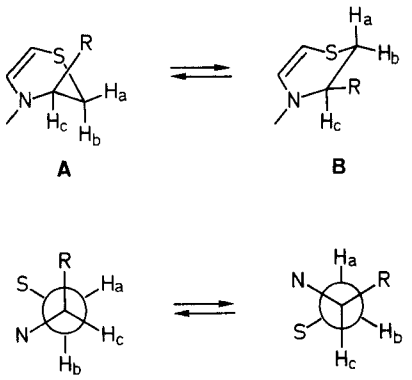
The data of compounds **4** and **5**, respectively, are collected in Tables 2, 3.

The study of the ^{1}H-NMR spectra of compounds **4** deserves further analysis.



4, 5	Ar	X	NR_2	4, 5	Ar	X	NR_2
a	Ph	CN	NMe_2	**g**	4-ClC_6H_4	COMe	NMe_2
b	Ph	COMe	NMe_2	**h**	4-ClC_6H_4	CO_2Me	NMe_2
c	Ph	CO_2Me	NMe_2	**i**	Ph	CHO	NMe_2
d	Ph	CO_2Me	piperidino	**j**	4-BrC_6H_4	CHO	NMe_2
e	4-BrC_6H_4	CN	NMe_2	**k**	4-ClC_6H_4	CHO	NMe_2
f	4-BrC_6H_4	COMe	NMe_2				

A study from Dunn and al.[11] on substituted 3,4-dihydro-2*H*-1,4-thiazines showed that these heterocycles can exist as the two following conformations.



These two conformations can be easily identified on the basis of the coupling constants values J_{ac} and J_{bc}. (conformation **A** $J_{ac} = J_{bc} = 3$ Hz, conformation **B** $J_{ac} = 9.8$ Hz, $J_{bc} = 3$ Hz). The values of the coupling collected in Table 2 seem to imply that the major conformer is the **A** one for compounds **4**.

Table 2. 3,4-Dihydro-2*H*-1,4-thiazines **4** Prepared

Product	Yield[a] (%)	R_f[b] (CH_2Cl_2)	Molecular Formula[c]	^{1}H-NMR ($CDCl_3$/TMS) δ, J (Hz)	MS *m/z*
4a	46	0.32	$C_{13}H_{15}N_3S$ (245.3)	2.62 (s, 6H), 3.10 (dd, 1H, J = 13.2, 3.4), 3.28 (dd, 1H, J = 13.2, 4.0), 4.75 (dd, J = 3.4, 4.0), 6.72 (s, 1H), 7.36 (m, 5H)	245 (M^+), 159 ($M^+ - HSCH_2CN$-CN)
4b	49	0.62	$C_{14}H_{18}N_2OS$ (262.3)	2.23 (s, 3H), 2.56 (s, 6H), 2.57 (dd, 1H, J = 12.7, 3.4), 3.35 (dd, 1H, J = 12.7, 4.3), 4.30 (dd, 1H, J = 3.4, 4.3), 6.96 (s, 1H), 7.30 (m, 5H)	262 (M^+), 159 ($M^+ - HSCH_2CH$-$COCH_3$
4c[f]	40	0.43	$C_{14}H_{18}N_2O_2S$ (278.3)	2.60 (s, 6H), 2.75 (dd, 1H, J = 12.7, 3.4), 3.40 (dd, 1H, J = 12.7, 4.2), 3.78 (s, 3H), 4.57 (dd, 1H, J = 3.4, 4.2), 6.96 (s, 1H), 7.27 (m, 5H)	278 (M^+), 159 ($M^+ - HSCH_2CH$-CO_2CH_3)
4d	37	0.45	$C_{17}H_{22}N_2O_2S$ (318.4)	1.49 (m, 6H), 2.69 (dd, 1H, J = 12.7, 3.4), 2.83 (m, 4H), 3.37 (dd, 1H, J = 12.7, 4.2), 3.75 (s, 3H), 4.58 (dd, 1H, J = 3.4, 4.2), 6.94 (s, 1H), 7.35 (m, 5H)	318 (M^+), 201 ($M^+ - HSCH_2CH$-CO_2CH_3)
4e	43	0.45	$C_{13}H_{14}BrN_3S$ (324.15)	2.63 (s, 6H), 3.10 (dd, 1H, J = 13.2, 3.4), 3.28 (dd, 1H, J = 13.2, 4.0), 4.77 (dd, 1H, J = 3.4, 4.0), 6.72 (s, 1H), 7.26, 7.42 (2d, 4H, ΣJ = 9)	323 (M^+),[d] 237 ($M^+ - HSCH_2CH$-CN)
4f	70	0.46[e]	$C_{14}H_{17}BrN_2OS$ (341.2)	2.21 (s, 3H), 2.50 (dd, 1H, J = 12.7, 3.6), 2.55 (s, 6H), 3.30 (dd, 1H, J = 12.7, 4.0), 4.29 (dd, 1H, J = 3.6, 4.0), 6.92 (s, 1H), 7.27, 7.38 (2d, 4H, ΣJ = 9)	340 (M^+),[d] 237 ($M^+ - HSCH_2CH$-$COCH_3$)
4g	47	0.47[e]	$C_{14}H_{17}ClN_2OS$ (296.7)	2.23 (s, 3H), 2.55 (s, 6H), 2.55 (dd, 1H, J = 12.7, 3.5), 3.35 (dd, 1H, J = 12.7, 4.2), 4.32 (dd, 1H, J = 3.5, 4.2), 6.93 (s, 1H), 7.26, 7.35 (2d, 4H, ΣJ = 8.5)	296 (M^+),[d] 194 ($M^+ - HSCH_2CH$-$COCH_3$)
4h	54	0.30	$C_{14}H_{17}ClN_2O_2S$ (312.7)	2.59 (s, 6H), 2.70 (dd, 1H, J = 12.7, 3.4), 3.40 (dd, 1H, J = 12.7, 3.9), 3.78 (s, 3H), 4.58 (dd, 1H, J = 3.4, 3.9), 6.92 (s, 1H), 7.24, 7.33 (2d, 4H, ΣJ = 9.3)	312 (M^+),[d] 194 ($M^+ - HSCH_2CH$-CO_2CH_3)

[a] Yield refers to pure isolated compounds.
[b] On plates silica gel MERCK 60 F_{254}.
[c] Satisfactory microanalyses obtained: C ±0.30, H ±0.25, N ±0.30.
[d] M^+ refers to ^{79}Br or ^{35}Cl
[e] Eluent: CH_2Cl_2/EtOAc (95 : 5).
[f] ^{13}C-NMR ($CDCl_3$/TMS): δ = 27.4 (t, CH_2S), 43.7 (q, $NCH_3)_2$), 52.4 (q, CH_3O), 59.1 (d, NCHCO), 125.4 (d, =CHN), 124.3, 124.5, 128.3 (d, CH_{arom}), 128.5 (s, =CS), 139.0 (s, C_{arom}), 170.6 (s, CO).

Table 3. 2*H*-1,4-Thiazines **5** Prepared

Product	Yield[a] (%)	mp (°C)	Molecular Formula[b]	^{1}H-NMR ($CDCl_3$/TMS) δ, J (Hz)	MS *m/z*
5b[d]	44	89–90	$C_{12}H_{11}NOS$ (217.2)	2.57 (s, 3H), 3.44 (s, 2H), 7.46 (m, 3H), 7.60 (m, 2H), 7.88 (s, 1H)	217 (M^+), 174 ($M^+ - COCH_3$)
5f	58	114–116	$C_{12}H_{10}BrNOS$ (296.1)	2.56 (s, 3H), 3.43 (s, 2H), 7.54 (s, 4H), 7.85 (s, 1H)	295 (M^+),[c] 252 ($M^+ - COCH_3$)
5g	54	97–99	$C_{12}H_{10}ClNOS$ (251.6)	2.55 (s, 3H), 3.42 (s, 2H), 7.40, 7.57 (2d, 4H, ΣJ = 8.5), 7.82 (s, 1H)	251 (M^+),[c] 208 ($M^+ - COCH_3$)
5i	26	–	$C_{11}H_9NOS$ (203.2)	3.42 (s, 2H), 7.47 (m, 3H), 7.65 (m, 2H), 7.98 (s, 1H), 9.76 (s, 1H)	203 (M^+), 174 ($M^+ - CHO$)
5j	39	122	$C_{11}H_8BrNOS$ (282.1)	3.41 (s, 2H), 7.54 (m, 4H), 7.96 (s, 1H), 9.76 (s, 1H)	281 (M^+),[c] 252 ($M^+ - CHO$)
5k	29	107–108	$C_{11}H_8ClNOS$ (237.6)	3.41 (s, 2H), 7.43, 7.59 (2d, 4H, ΣJ = 8.6), 7.94 (s, 1H) 9.75 (s, 1H)	237 (M^+),[c] 208 ($M^+ - CHO$)

[a] Yield refers to pure isolated compounds.
[b] Satisfactory microanalyses obtained: C ±0.20, H ±0.20, N ±0.20.
[c] M^+ refers to ^{79}Br or ^{35}Cl.
[d] ^{13}C-NMR ($CDCl_3$/TMS): δ = 20.3 (q, CH_3), 25.2 (t, CH_2S), 129.0, 130.0 (d, CH_{arom}), 132.1 (d, =CHN), 133.4, (s, =CS), 135.9 (s, C_{arom}), 142.9 (s, N=CCO), 198.4 (s, CO).

In conclusion, it is possible to prepare unstable (hydrazono) thioketones by thionation of the corresponding carbonyl compounds. These new heteroatomic chains can be used as building blocks in heterocyclic synthesis which has allowed us to describe an original approach to 3,4-dihydro-2*H*-1,4-thiazines and 2*H*-1,4-thiazines via [4 + 2] cycloaddition reaction.

All reagents were purchased from Jansen Chimica Co. Kieselgel 60 (70–230 mesh) from E. Merck was used for silica gel column chromatography. Melting points were taken using Reichert microscope and are uncorrected. ^{1}H-NMR spectra were obtained using a JEOL FX90Q 90 MHz spectrometer. Mass spectra were obtained using a Varian Mat 112 spectrometer.

2-(Dialkylhydrazono)acetophenones 2; General Procedure:
1,1-Dimethylhydrazine (20 mmol) is added dropwise to a solution

of arylglyoxal hydrate **1** (20 mmol) in EtOH (50 mL). After 24 h stirring at r.t., EtOH is evaporated under reduced pressure. The residue is then diluted with CH_2Cl_2 (10 mL) and fractionated by silica gel chromatography. After elution using CH_2Cl_2/EtOAc (80:20) compounds **3** are isolated as yellow oil

2-(Dialkylhydrazono)thioacetophenones 3; General Procedure:
Lawesson's reagent (2.5 mmol) is added to a solution of 2-(dialkylhydrazono)acetophenone **2** (5 mmol) in benzene (2 mL) at 10 °C under inert atmosphere (N_2). After 5 min stirring the mixture is allowed to warm to r.t. (10 min). The solution is then diluted with benzene (6 mL) and fractionated by silica gel column chromatography. After elution using petroleum ether (bp 55–60 °C)/EtOAc (80:20) compounds **3** are isolated as a dark green oil.

3,4-Dihydro-2*H*-1,4-thiazines 4b,f,g; General Procedure:
Methyl vinyl ketone (20 mmol) is added to a solution of **3** (5 mmol) in benzene (2 mL) containing some hydroquinone crystals. After 5 h stirring at r.t., the mixture is evaporated under reduced pressure, diluted with benzene (10 mL) and fractionated by silica gel column chromatography. After elution using CH_2Cl_2/EtOAc (95:5), compounds **4b,f,g** are isolated as a yellow oil (Table 2).

3,4-Dihydro-2*H*-1,4-thiazines 4a,c,d,e,h; General Procedure:
A solution of compound **3** (5 mmol) in methyl acrylate or acrylonitrile (50 mmol) containing some hydroquinone crystals is stirred 20 h at r.t. The mixture is then treated as above. Compounds **4a,c,d,e,h** are isolated as a yellow oil (Table 2).

2*H*-1,4-Thiazines 5b,f,g; General Procedure:
Corresponding compound **4** is heated at 60 °C for 3 h under reduced pressure (10 mmHg). The residue is then diluted with benzene and fractionated by silica gel column chromatography. After elution using CH_2Cl_2, compounds **5b,f,g** are crystallized in a mixture of petroleum ether (bp 55–60 °C)/Et_2O (Table 3).

2*H*-1,4-Thiazines 5i–k; General Procedure:
Acrolein (3 mmol) is added to a solution of compound **3** (1,5 mmol) in benzene (2 mL) containing some hydroquinone crystals. After 2 h stirring at room temperature, the mixture is heated up to 40 °C for 2 h and then fractionated by silica gel column chromatography. After elution using CH_2Cl_2, compounds **5i–k** are crystallised in a mixture of petroleum ether/Et_2O. Compound **5i** is isolated as a yellow oil (Table 3).

Received: 22 October 1990; revised: 19 February 1991

(1) Reliquet, A.; Reliquet, F.; Meslin, J.C.; Sharrard, F.; Benhadda, D.; Toupet, L. *Phosphorus sulfur silicon* **1989**, *44*, 87.
(2) Quiniou, H. *Phosphorus Sulfur* **1981**, *10*, 1.
(3) Meslin, J.C.; N'Guessan, Y.T.; Quiniou, H.; Tonnard, F. *Tetrahedron* **1975**, *31*, 2679.
(4) Meslin, J.C.; Reliquet, A.; Reliquet, F.; Tea Gokou, C. *C.R. Acad. Sci.* **1978**, *286(C)*, 397.
(5) Meslin, J.C.; Quiniou, H. *Tetrahedron* **1975**, *31*, 3055.
(6) Meslin, J.C.; Quiniou, H. *Bull. Soc. Chim. Fr.* **1979**, *II*, 347.
(7) Reliquet, A.; Meslin, J.C.; Reliquet, F.; Quiniou, H. *Tetrahedron* **1988**, *44(4)*, 1107.
(8) Bakasse, M.; Reliquet, A.; Reliquet, F.; Duguay, G.; Quiniou, H. *J. Org. Chem.* **1989**, *54*, 2889.
(9) Kamitori, Y.; Hojo, M.; Masuda, R.; Kawamura, Y.; Numai, T. *Synthesis* **1990**, 491.
(10) Kornblum, N.; Frazier, H.W. *J. Am. Chem. Soc.* **1966**, *88*, 865.
(11) Dunn, A.R.; Stoodley, R.J. *Tetrahedron* **1972**, *28*, 3315.