Tetrahedron Letters,Vol.27,No.51,pp 6185-6188,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

REACTIVITY ENHANCEMENT THROUGH STRAIN AND ELECTRONIC EFFECTS: α-HETEROCYCLOPROPYLIDENACETATES AS POWERFUL MICHAEL ACCEPTORS

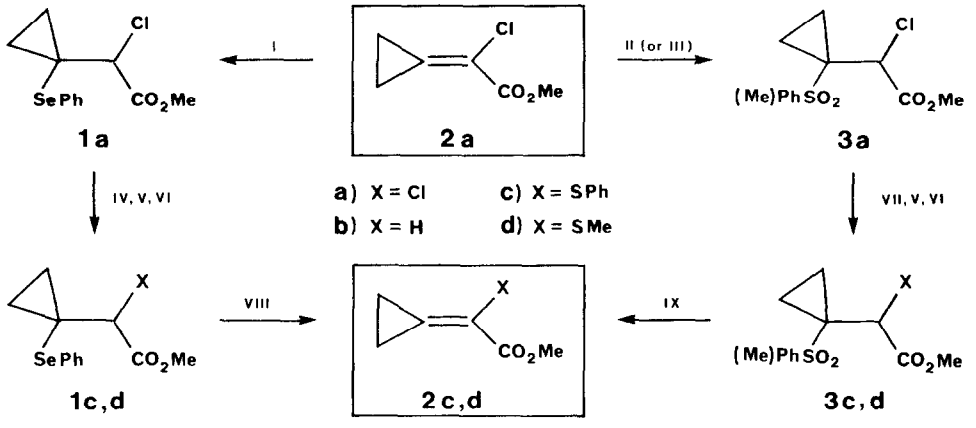
*Fereydoun Seyed-Mahdavi, Stephan Teichmann and Armin de Meijere**

Institut für Organische Chemie der Universität Hamburg,
Martin-Luther-King-Platz 6, D-2000 Hamburg 13, W.-Germany

*Abstract: The new α-thiosubstituted cyclopropylidenacetates **2c,d** have been synthesized from **2a**. The relative reactivities of **2a,b,c,d**, their substituted analogues **4a** and 3,3-dimethylacrylate (**7**) towards thiophenolate were determined by competition experiments. Both ring strain and α-heterosubstituents drastically enhance the reactivity. **2c** readily undergoes cycloaddition to cyclopentadiene and addition of carbon nucleophiles at room temperature.*

α-Chlorocyclopropylidenacetates **2a**, which are readily accessible from 1-chloro-1-(trichlorovinyl)cyclopropanes,[1] have proven to be useful building blocks for the construction of various bi- and tricyclic skeletons.[2,3,4] As the α-chlorosubstituent may be undesirable in certain applications, we have engaged in a search for cyclopropylidenacetates with other α-substituents and tested their relative reactivity in comparison to that of **2a** and methyl 3,3-dimethylacrylate (senecioester).

To modify **2a**, a three-step sequence was envisaged (see scheme 1).



Scheme 1. Transformations of **2a** to **2b,c,d** (for conditions see table 1).

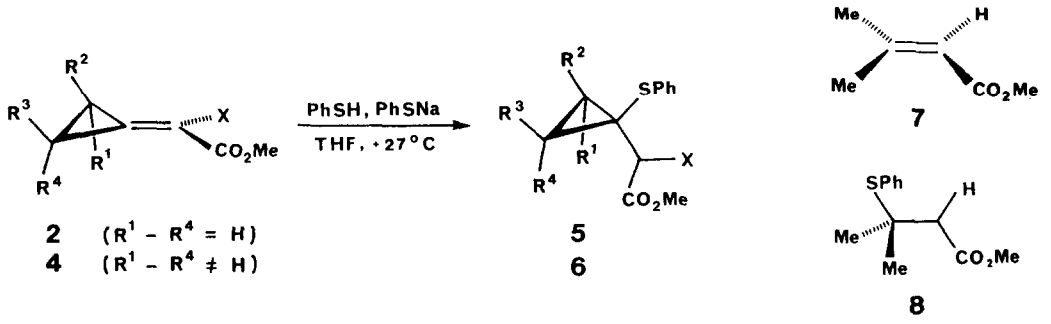
Sodium phenylselenide added to **2a** at -78°C and gave **1a** in practically quantitative yield (see table 1). **1a** readily underwent nucleophilic substitution at the cyclopropylcarbinyl position with phenyl- and methylmercaptan under thiolate catalysis to yield **1c,d**, but t-butylmercaptan caused formal reduction to **1b**. Oxidation of the (phenylselenocyclopropyl)acetates **1b,c**, with m-chloroperbenzoic acid (m-CPBA) followed by sodium carbonate work-up yielded the β-elimination products under mild conditions.[5] The new α-thiocyclopropylidenacetate **2c** and the known parent compound **2b** were thus obtained in very good overall yields.[6]

Alternatively, sodium p-toluenesulfenate or benzenesulfenate was added to **2a** in a two-phase system under TEBA (triethylbenzylammonium chloride) catalysis to give **3a**, which was substituted with PhS^- and MeS^- or reduced with zinc-copper couple in aqueous tetrahydrofuran under ultrasonification[7] to yield **3b,c,d**. β-Elimination was best achieved in these compounds with a solid-liquid phase transfer system consisting of powdered potassium hydroxide, methylene chloride and dibenzo-[18]crown-6.[8] The overall yields of **2b,c,d** in this sequence were not quite as good as the ones via **1b,c**, (see table 1).

Table 1. Reaction conditions, yields and product characterization in the conversion of **2a** to cyclopropylidenacetates **2b,c,d**.

Educt	Reaction conditions	Prod.[a]	Yield [%]	M.p. [°C]	IR[b] [cm^{-1}]
2a	I: NaSePh,EtOH,-78°C,3h	**1a**	95-100	-[c]	1740
1a	IV: t-BuSH,t-BuSNa(trace),DMSO,RT,10min	**1b**	83	29	1730
1b	VIIa: 1)m-CPBA,$CHCl_3$,-5-0°C; 2)Na_2CO_3	**2b**	93	127[d]	1700
1a	Va: PhSH/PhSNa(10:1.5),DMSO,RT,15min	**1c**	95-100	-[c]	1720
1c	VIIIb: 1)m-CPBA,$CHCl_3$,-15°C,10min;2)Na_2CO_3	**2c**	89- 95	-[c]	1700
1a	VIa: MeSH,MeSNa(30:2),HMPA,RT,10min	**1d**	86	-[c]	1720
2a	II: $PhSO_2Na$,H_2O/CH_2Cl_2,TEBA,5°C,24h	**3a**	54	51	1750
2a	III: $MePhSO_2Na$,H_2O/CH_2Cl_2,TEBA,5°C,4h	**3a**(Me)	62	78	1760
3a(Me)	VII: Zn-Cu,THF/H_2O(99:1),RT,U.S.,20min	**3b**(Me)	94	-[c]	1735
3b(Me)	IXa: KOH,CH_2Cl_2,DB-18-C-6,U.S.,20min	**2b**	73	127[d]	1700
3a	Va: PhSH/PhSNa(10:1),DMSO,RT,10min	**3c**	90	-[c]	1730
3a(Me)	Vb: PhSH/PhSNa(10:1),HMPA,RT,10min	**3c**(Me)	66	-[c]	1725
3c	IXa: KOH,CH_2Cl_2,DB-18-C-6(tr.),RT,U.S.,30min	**2c**	81	-[c]	1700
3c(Me)	IXb: KOH,CH_2Cl_2,DB-18-C-6(tr.),RT,U.S.,55min	**2c**	81	-[c]	1700
3a(Me)	VIb: MeSH,MeSNa(100:1),DMSO,14-18°C,30min	**3d**(Me)	62	63	1730
3d(Me)	IXa: KOH,CH_2CL_2,DB-18-C-6(tr.),RT,U.S.,15min	**2d**	65	49	1700

[a] **2b** was purified by distillation, all others by column chromatography over silica gel. [b] All new compounds were fully characterized also by ^1H NMR, ^{13}C NMR, MS as well as elemental analysis or molecular mass determination (high resolution MS). [c] Oil. [d] B.p..



2 ($R^1 - R^4 = H$)
4 ($R^1 - R^4 \neq H$)

5
6

7

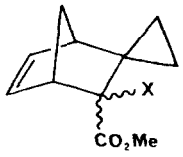
8

Scheme 2.

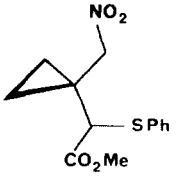
The relative reactivities of these cyclopropylidenacetates **2a,b,c,d** as well as their substituted analogues **4a**[1] toward nucleophiles were determined by letting pairs of them compete for thiophenolate at +27°C under high dilution conditions.[9] The results (see table 2) show that both the presence of the strained ring (as in **2b**) and the heterosubstituents (as in **2a,c,d**) increase the reactivity by up to a factor of 5160 over that of methyl 3,3-dimethylacrylate **7**. Methyl substituents on the ring, however, apparently cause more or less steric hindrance to the nucleophilic attack at the β-carbon and decrease the relative reactivity up to 215 fold.

Table 2. Competition factors for the Michael additions of thiophenolate to cyclopropylidenacetates **2a,b,c,d**, **4a** and 3,3-dimethylacrylate **7**.

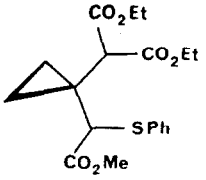
Compd.	Y	R^1	R^2	R^3	R^4	Prod.	Compet. with		Compet. factors		
2a	Cl	H	H	H	H	**5a**	$\mathbf{4a}_5$		86		215
2b	H	H	H	H	H	**5b**	**2a**		0.08		18
2c	SPh	H	H	H	H	**5c**	**2a**		24		5160
2d	SMe	H	H	H	H	**5d**	**2a**		9		1930
7	-	H	H	H	H	**8**	$\mathbf{4a}_5$		0.4		1.0
$\mathbf{4a}_1$	Cl	Me	H	H	H	$\mathbf{6a}_1$	$\mathbf{4a}_5$		41		103
$\mathbf{4a}_2$	Cl	H	Me	Me	H	$\mathbf{6a}_2$	$\mathbf{4a}_5$	**2a**	42	2.5	105
$\mathbf{4a}_3$	Cl	H	Me	H	Me	$\mathbf{6a}_3$	$\mathbf{4a}_5$	**2a**	17	2.1	43
$\mathbf{4a}_4$	Cl	Me	Me	Me	H	$\mathbf{6a}_4$	$\mathbf{4a}_5$		10		25
$\mathbf{4a}_5$	Cl	Me	Me	Me	Me	$\mathbf{6a}_5$	$\mathbf{4a}_5$		1.0		2.5



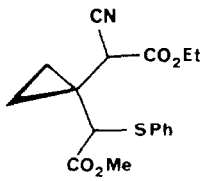
9a X = Cl
9b X = H
9c X = SPh



10



11



12

The reactivity of the new α-phenylthiocyclopropylidenacetate (**2c**) as a dienophile is about the same as that of the α-chloro derivative **2a**.[2] Both cycloadded to cyclopentadiene at room temperature to give 81% **9c** (endo/exo = 1.4) and 91% **9a** (endo/exo = 2.8)[2,4] respectively within 4 h, while the unsubstituted compound **2b** required ~4 d to react completely yielding 81% **9b** (endo/exo = 3.3).

The utility of **2c** in C,C-bond forming Michael additions was demonstrated with three different carbon nucleophiles. Nitromethane in benzene in the presence of potassium fluoride, diisopropylamine and dibenzo[18]-crown-6,[10] gave a 96% isolated yield of **10** after 16 h at room temperature. Similarly, diethyl malonate and ethyl cyanoacetate added to yield 69% **11** and 42% **12** respectively (non-optimized) after 1 - 3 h.

References and footnotes.

This work was supported by the Deutsche Forschungsgemeinschaft (Grant Me 405/14-1), the Fonds der Chemischen Industrie, Hoechst AG and Chemische Werke Hüls AG.

1 Th. Liese, G. Splettstösser, A. de Meijere, Angew. Chem., 94, 799 (1982); Angew. Chem. Int. Ed. Engl. 21, 790 (1982); Angew. Chem. Suppl. 1982, 1715.

2 D. Spitzner, A. Engler, Th. Liese, G. Splettstösser, A. de Meijere, Angew. Chem. 94, 799 (1982); Angew. Chem. Int. Ed. Engl. 21, 791 (1982); Angew. Chem. Suppl. 1982, 1722.

3 See also: A. de Meijere, Bull. Soc. Chim. Belges 93, 241 (1984).

4 D. Spitzner, G. Bengtson, A. de Meijere, to be published.

5 Cf. H.J. Reich, J.M. Renga, I.L. Reich, J. Am. Chem. Soc. 97, 5434 (1975); H.J. Reich, S.K. Shah, ibid. 97, 3250 (1975); K.B. Sharpless, K.M. Gordon, R.F. Lauer, D.W. Patrick, S.P. Singer, M.W. Young, Chem. Scr. 8A, 9 (1975).

6 The ethyl ester corresponding to **1b** has previously been prepared only with poor yield: J. Salaün, F. Bennani, J.-C. Compain, A. Fadel, J. Ollivier, J. Org. Chem. 45, 4129 (1980). More recently, however, its preparation has been drastically improved: D. Spitzner, H. Swoboda, Tetrahedron Lett. 27, 1281 (1986).

7 For other examples of ultrasound activation cf. B.-H. Han, P. Boudjouk, J. Org. Chem. 47, 751, 5030 (1982).

8 Cf. S. Keyaniyan, M. Apel, J.P. Richmond, A. de Meijere, Angew. Chem. 97, 763 (1985); Angew. Chem. Int. Ed. Engl. 24, 770 (1985).

9 Cf. T.S. Lee in S.L. Friess, A. Weissberger: Technique in Organic Chemistry, Interscience, New York 1953, Vol. III, p. 100-130.

10 Conditions as employed by: I. Belsky, J. Chem. Soc., Chem. Commun. 1977, 237.

(Received in Germany 6 February 1986; accepted 30 September 1986)