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The Reaction of Cyclic Olefins with Chloromethyl Methyl Sulfide in Acetonitrile

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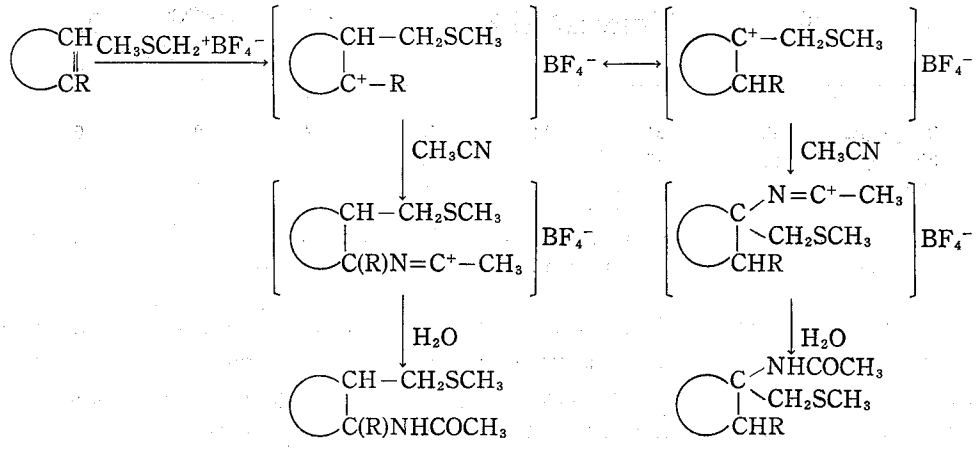
In the presence of $AgBF_4$, some cyclic olefins reacted with chloromethyl methyl sulfide and acetonitrile to afford the products of three-component reaction in which three reactants successively combine.

KEY WORDS: Reaction of cyclic olefins/ Reaction of chloromethyl methyl sulfide/ Reaction of acetonitrile/

In a previous paper[1] we reported that the Lewis acid-catalyzed reaction of olefins with chloromethoxymethane and nitriles afforded the 1: 1: 1 adducts and/or their hydrolysis products in various yields, together with the 1: 1 olefin-chloromethoxymethane adducts. When chloromethyl methyl sulfide was used instead of chloromethoxymethane, the reaction took place only with cyclic olefins under the catalytic action of $AgBF_4$ leading to 1- and 2-methylthiomethylated N-cycloalkylacetamides (**2** and **1**) as well as some by-products formed by the ordinary two-component reactions. Both **1** and **2** are the products of three-component reaction in which three reactants successively combine, as represented by the following equation.



1 **2**

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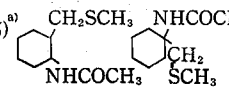
It is known[2] that the strongly polarized complexes of general formula X^+Y^-, where X^+ is a cationoid species such as an alkyl- and acyl-cation, and Y^- is a strong acid anion, *e.g.*, BF_4^- or SbF_6^-, are the useful reagents for electrophilic addition reaction. From these known data it seems reasonable to propose that the initial step of the present reaction is the formation of methylthiomethyl tetrafluoroborate, which belongs to the above-mentioned complexes. Thus, the mechanism of the reaction has been thought to involve electrophilic attack of the methylthiomethyl tetrafluoroborate to a cyclic olefin and subsequent reaction of the carbonium ion thus produced with acetonitrile to give **1**. When the carbonium ion undergo 1, 2-rearrangement, the nucleophilic attack of acetonitrile occurs on the same carbon that methylthiomethyl-cation has attacked, leading to the product, **2**.

When the above reaction was examined on cyclohexene at room temperature, in either the presence or absence of nitromethane, the main products were the following compounds: N-(2-methylthiomethylcyclohexyl)acetamide (**1a**), N-(1-methylthio-methylcyclohexyl)acetamide (**2a**), 3-methylthiomethylcyclohexene (**3**) and N-cyclohexylacetamide (**4**). The former two are the 1: 1: 1 adducts. When $ZnCl_2$ was used in place of $AgBF_4$, none of the 1: 1: 1 adducts was found at least under the given conditions. Some typical data of the reaction with cyclohexene are given in Table I.

Table I. Reaction of Cyclohexene with Chloromethyl Methyl Sulfide in Acetonitrile

Chloromethyl methyl sulfide, 50 mmol; Cyclohexene, 50 mmol; Acetonitrile, 1 mol; Catalyst, 50 mmol; Nitromethane, 41 ml. Reaction conditions: 20–25°C, 24 h.

Run	Catalyst	Total yield(%)[a] of 1:1:1 and 1:1 adducts	Product distribution (mol %)					
								
			1a	**2a**	**3**	**4**	**5**	**6**
1[b]	$AgBF_4$	16	16	10	63	11	0	0
2	$AgBF_4$	12	24	14	58	4	0	0
3[c]	$AgBF_4$	27	27	10	57	6	0	0
4[b]	$ZnCl_2$	39	0	0	59	10	5	26

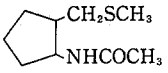
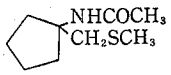
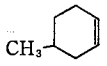
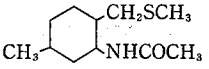
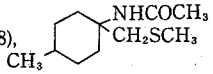
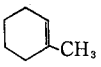
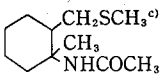
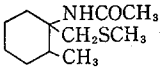
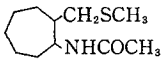
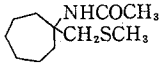
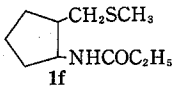
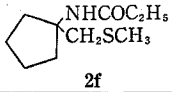
a) Yield is based upon cyclohexene, and is of the isolated products by column chromatography.
b) Nitromethane was omitted. c) Reaction time: 72 h.

Although the yields of 1: 1: 1 adducts are relatively low, this example demonstrates the usefulness of this reaction as a method for one-step transformation of cyclohexene into the bifunctional cyclohexane derivatives, not readily, if at all, obtainable by other procedures. It has been found that this procedure is also successful in cases where cyclopentene, 4-methylcyclohexene and 1-methylcyclohexene as well as cycloheptene are used as an olefin component. The total yield of the 1: 1: 1 adducts and their compositions in these reactions are shown in Table II.

As can be seen from Table II, the use of 4-methylcyclohexene in the reaction leads to the formation of N-(5-methyl-2-methylthiomethylcyclohexyl)acetamide (**1c**)

Table II. Preparation of N-(2-Methylthiomethylcycloalkyl)acetamides (**1**) and N-(1-Methylthiomethylcycloalkyl)acetamides (**2**)

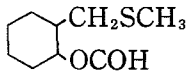
Chloromethyl methyl sulfide, 50 mmol; Cyclic olefin, 50 mmol; Acetonitrile, 1 mol; $AgBF_4$, 50 mmol; Nitromethane, 41 ml. Reaction conditions: 20–25°C, 72 h.

Run[a]	Olefin	Total yield[b](%) of 1:1:1 adducts	Composition of 1:1:1 adducts (mol %)			
1		14	 **1b**	(71),	 **2b**	(29)
2		11	 **1c**	(68),	 **2c**	(32)
3		17	 **1d**	(76),	 **2d**	(24)
4		10	 **1e**	(55),	 **2e**	(45)
5[d]		14	 **1f**	(64),	 **2f**	(36)

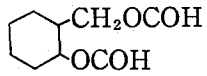
a) The isolation of the products formed by the ordinary two-component reactions was not put in practice. b) The yield represents pure compound isolated by column chromatography. c) A mixture of *cis*- and *trans*-isomers in an approximate ratio of 1: 6. d) One mol of ethyl cyanide was used instead of 1 mol of acetonitrile under otherwise identical conditions.

and N-(4-methyl-1-methylthiomethylcyclohexyl)acetamide (**2c**), suggesting that methylthiomethyl-cation should add preferentially to the 1-position of 4-methylcyclohexene in the initial stage of the reaction. With 1-methylcyclohexene as an olefin component, the addition of the cation occurs in the 2-position, explaining the formation of N-(1-methyl-2-methylthiomethylcyclohexyl)acetamide (**1d**) and N-(2-methyl-1-methylthiomethylcyclohexyl)acetamide (**2d**) as 1: 1: 1 adducts.

When cyclohexene was allowed to react with chloromethyl methyl sulfide and excess formic acid in ether at room temperature for 24 h, in the presence of either $AgBF_4$ or $ZnCl_2$, 1-formyloxy-2-(methylthiomethyl)cyclohexane (**7**) and 1-formyloxy-2-(formyloxymethyl)cyclohexane (**8**) were obtained.



7



8

The formation of **7** may be explained by a mechanism which involves initial attack of methylthiomethyl-cation on cyclohexene to form a transient carbonium ion and its subsequent reaction with formic acid. Chloromethyl methyl sulfide should undergo a formolysis reaction to afford methylthiomethyl formate similar to that observed with chloromethoxymethane.[3] The electrophilic attack of formyloxymethyl-cation, which arise from the above methylthiomethyl formate, to cyclohexene, followed by nucleophilic attack of formic acid will give **8**, probably idnetical to that previously reported as *trans*-isomer.[3]

Table III. Reaction of Cyclohexene with Chloromethyl Methyl Sulfide and Formic Acid

Chloromethyl methyl sulfide, 50 mmol; Cyclohexene, 50 mmol; Catalyst, 50 mmol; Formic acid, 0.5 mol; Ether, 30 ml. Reaction conditions: 20–25°C, 24 h.

Run[a]	Catalyst	Total yield[b] (%) of **7** and **8**	Composition (mol %)	
1	$AgBF_4$	11	**7** (51),	**8** (49)
2	$ZnCl_2$	10	**7** (80),	**8** (20)

a) The yield represents pure compound isolated by column chromatography.
b) The products formed by the ordinary two-component reactions were not isolated.

Table IV. Physical Properties and Analytical Data of Methylthiomethylated N-Cycloalkylacetamides

Product[a]	Mp (°C)	^{1}H-NMR, δ(ppm from TMS, in $CDCl_3$)	Found (calcd), %		
			C	H	N
1a	117–120	6.7–6.3 (m, 1H), 3.9–3.3 (m, 1H), 2.8–2.2 (m, 2H), 2.09 (s, 3H), 1.95 (s, 3H), 2.0–1.0 (m, 9H)	59.84 (59.66)	9.85 (9.51)	6.64 (6.96)
2a	102–104	5.5–5.3 (m, 1H), 2.98 (s, 2H), 2.09 (s, 3H), 1.95 (s, 3H), 2.0–1.0 (m, 10H)	59.96 (59.66)	9.68 (9.51)	6.74 (6.96)
1b	66–70	7.2–6.9 (m, 1H), 4.1–3.7 (m, 1H), 2.9–2.4 (m, 2H), 2.10 (s, 3H), 1.97 (s, 3H), 2.7–1.0 (m, 7H)	57.92 (57.72)	9.20 (9.15)	7.17 (7.48)
2b	58–61	6.1–5.8 (m, 1H), 3.02 (s, 2H), 2.11 (s, 3H), 1.93 (s, 3H), 2.0–1.5 (m, 8H)	57.39 (57.72)	9.28 (9.15)	7.24 (7.48)
1c	—[b]	7.2–6.8 (m, 1H), 4.1–3.6 (m, 1H), 2.8–2.2 (m, 2H), 2.05 (s, 3H), 1.98 (s, 3H), 2.0–1.0 (m, 8H), 0.95 (d, 3H)	61.07 (61.35)	9.71 (9.83)	6.20 (6.51)
2c	—[b]	5.8–5.5 (m, 1H), 2.94 (s, 2H), 2.07 (s, 3H), 1.92 (s, 3H), 2.0–1.0 (m, 9H), 1.1–0.8 (m, 3H)	60.94 (61.35)	9.99 (9.83)	6.32 (6.51)

cis-**1d**	77–79	5.8–5.5 (m, 1H), 2.9–2.4 (m, 2H), 2.12 (s, 3H), 1.94 (s, 3H), 2.0–1.0 (m, 9H), 1.48 (s, 3H)	61.17 (61.35)	9.81 (9.83)	6.21 (6.51)
trans-**1d**	95–99	5.7–5.3 (m, 1H), 2.8–2.3 (m, 2H), 2.08 (s, 3H), 1.94 (s, 3H), 2.0–1.0 (m, 9H), 1.22 (s, 3H)	61.11 (61.35)	9.94 (9.83)	6.28 (6.51)
2d	74–77	5.8–5.4 (m, 1H), 3.2–2.6 (m, 2H), 2.10 (s, 3H), 1.95 (s, 3H), 2.0–1.1 (m, 9H), 0.92 (d, 3H)	61.09 (61.35)	9.80 (9.83)	6.33 (6.51)
1e	71–73	7.0–6.6 (m, 1H), 4.0–3.5 (m, 1H), 2.8–2.3 (m, 2H), 2.03 (s, 3H), 1.95 (s, 3H), 2.0–1.0 (m, 11H)	61.65 (61.35)	9.98 (9.83)	6.38 (6.51)
2e	67–71	5.4–5.1 (m, 1H), 3.00 (s, 2H), 2.05 (s, 3H), 1.90 (s, 3H), 2.0–1.0 (m, 12H)	61.57 (61.35)	10.13 (9.83)	5.94 (6.51)

a) The stereochemical assignment for these products could not be established except **1d**. In cases where stereoisomers are possible they are probably either the pure *trans*-isomers or the mixture in which the major *trans*-isomer is accompanied by relatively small amounts of the *cis*-isomer. b) Mp could not be determined because of the limited amounts.

Table V. Physical Properties and Analytical Data of the Products other than Methylthiomethylated N-Cycloalkylacetamides

Product[a]	Mp (°C) or bp (°C/torr)	^{1}H-NMR, δ(ppm from TMS, in $CDCl_3$)	Found (calcd), %		
			C	H	N
1f	80–81	6.7–6.2 (m, 1H), 4.2–3.7 (m, 1H), 2.9–2.4 (m, 2H), 2.3–2.1 (m, 2H), 2.08 (s, 3H), 2.0–1.0 (m, 7H), 1.13 (t, 3H)	59.40 (59.66)	9.64 (9.51)	6.94 (6.96)
2f	68–71	6.1–5.7 (m, 1H), 3.00 (s, 2H), 2.3–2.1 (m, 2H), 2.06 (s, 3H), 2.0–1.2 (m, 8H), 1.07 (t, 3H)	59.37 (59.66)	9.36 (9.51)	6.69 (6.96)
3	105/34–35	5.63 (s, 2H), 2.43 (s, 2H), 2.10 (s, 3H), 1.9–1.0 (m, 7H)	67.19 (67.54)	10.10 (9.92)	
4	105 (lit,[4] 106–107°C)	5.9–5.5 (m, 1H), 3.9–3.5 (m, 1H), 1.94 (s, 3H), 2.0–1.0 (m, 10H)	67.83 (68.04)	10.50 (10.71)	9.62 (9.92)
5	—[b]	3.9–3.6 (m, 1H), 3.1–2.3 (m, 2H), 2.12 (s, 3H), 1.9–1.0 (m, 9H)	53.80 (53.77)	8.51 (8.46)	
6	—[b]	4.0–3.6 (m, 1H), 2.42 (d, 2H), 2.08 (s, 3H), 2.0–1.0 (m, 9H)	53.98 (53.77)	8.68 (8.46)	
7	—[b]	7.97 (s, 1H), 5.0–4.5 (m, 1H), 3.0–2.3 (m, 2H), 2.03 (s, 3H), 2.0–1.0 (m, 9H)	57.69 (57.41)	8.71 (8.57)	
8	—[b]	8.00 (s, 2H), 5.0–4.5 (m, 1H), 4.10 (d, 2H), 2.0–1.0 (m, 9H)	58.20 (58.05)	7.80 (7.58)	

a) The stereochemical assignment for these products could not be established. b) Mp or bp could not be determined because of the limited amounts.

EXPERIMENTAL

Reaction of Cyclic Olefin with Chloromethyl Methyl Sulfide in Acetonitrile. To a stirred mixture of 50 mmol of a cyclic olefin, 1 mol of acetonitrile, 50 mmol of a catalyst ($AgBF_4$ or $ZnCl_2$) and 41 ml of nitromethane (which was omitted in Runs 1 and 4 in Table I) was added dropwise 50 mmol of chloromethyl methyl sulfide, the temperature being maintained at near 0°C. The mixture was then stirred for either 24 h or 72 h at room temperature (20–25°C), poured into a large quantity of cold water, and then stirred vigorously for 1 h. The precipitated substance was removed by filtration and washed with ether, the ether being combined with an ethereal extract of the filtrate. The organic layer was washed with dilute aqueous K_2CO_3, then with brine, dried ($MgSO_4$) and evaporating the solvents gave a residue. The products were isolated from the residue by column chromatography on silica gel using hexane-ether or hexane-dichloromethane as eluent.

Reaction of Cyclohexene with Chloromethyl Methyl Sulfide and Formic Acid. To a stirred mixture of 50 mmol of cyclohexene, 0.5 mol of formic acid, 50 mmol of a catalyst ($AgBF_4$ or $ZnCl_2$) and 30 ml of ether was added dropwise 50 mmol of chloromethyl methyl sulfide at 0–5°C. The mixture was brought to room temperature, stirred for 24 h and then poured slowly into a suspension of $CaCO_3$ in water. After stirring for 1 h, the mixture was extracted with several portions of ether. The combined ethereal extract was washed with brine and water, dried over anhydrous $MgSO_4$, and the solvent was evaporated under reduced pressure. Chromatography on a silica column using hexane-ether or hexane-dichloromethane as eluent gave the objective products.

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