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Catalytic multicomponent thiomethylation of aliphatic 1,3-diketones as efficient one-pot synthesis of novel bis(1,3-diketone-2-ylmethylsulphanyl)alkanes

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α,ω-Dithiols

ABSTRACT

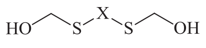
A catalytic method for the selective synthesis of novel bis(1,3-diketone-2-ylmethylsulfanyl)alkanes via the thiomethylation reactions of aliphatic 1,3-diketones with CH_2O and α,ω-dithiols is provided. Selective cyclothiomethylation of 1-phenylbutane-1,3-dione has been realized using a tandem catalyst $Cp_2Zr(Ti)Cl_2$-BuONa to form 6-benzoyl-1,4-dithiepane. Proposed mechanisms of catalytic thiomethylation reactions are also discussed.

1. Introduction

Sulfur-containing carbonyl compounds are of interest as building blocks for fine organic synthesis[1] and polydentate ligands of coordination compounds using in supramolecular and polymer chemistry.[2] It's known that the alkylsulfanyl groups are formed in multicomponent reactions (MCRs) of NH-, OH-, SH- and CH-acids with formaldehyde and *S*-nucleophiles.[3] Furthermore the thiomethylation of carbonyl-containing CH-acids can be implemented with the use of aldehydes, mercaptanes and various activators. These MCRs are realized in neutral-[4a] or alkaline medium[4b,c] and in the presence of different catalysts as well.[4d–f] It should be noted that MCRs, which minimize waste formation are worldwide trend in Green chemistry.[5]

Recently we have established that dimethyl malonate reacts as a CH-acid with CH_2O and 1,2-ethanedithiol in the presence of Lewis acids (5 mol %) to form 6,6-di(metoxycarbonyl)-1,4-dithiepane in 70–80% yield,[6a] while 2,4-pentandione reacts under these conditions to give open-chain 1,2-bis[(pentane-2,4-dione-3-yl)methylsulfanyl]ethane in 59% yield.[6b]

In order to study the scope of the multicomponent thiomethylation of 1,3-diketones in the one-pot synthesis of novel bis[(1,3-diketone-2-yl)methylsulphanyl]alkanes, we have investigated the reactivity of aliphatic and aromatic 1,3-diketones **1a–g**. We used a 2:1 mixture of CH_2O and α,ω-dithiol HS(X)SH [X=$(CH_2)_{2-6}$, $((CH_2)_2S(CH_2)_2)$] as thiomethylation agent, which forms in situ appropriate formaldehyde hemithioacetals **2a–f** (Fig. 1).



2a-f
X = $(CH_2)_2$ (**2a**), $(CH_2)_3$ (**2b**), $(CH_2)_4$ (**2c**), $(CH_2)_5$ (**2d**), $(CH_2)_6$ (**2e**), $((CH_2)_2S(CH_2)_2)$ (**2f**)

Fig. 1. The structure of formaldehyde hemithioacetals **2a–f**.

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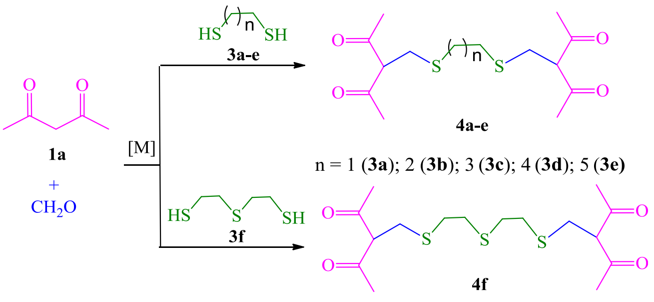
2. Results and discussion

2.1. Multicomponent thiomethylation of aliphatic 1,3-diketones 1a–e

Using the thiomethylation reaction of 2,4-pentanedione 1a with CH_2O and 1,2-ethanedithiol as an example, we have examined methylene-activating Lewis and silica-alumina catalysts. In all experiments, 1,2-bis[(pentane-2,4-dione-3-yl)methylsulfanyl]ethane **4a** was formed regioselectively (Scheme 1) with the yield dependent on the catalyst and solvent. Thus, MCRs effectively proceed at rt in chloroform/ethanol (1:1) media via interaction of diketone **1**a with a preliminarily obtained mixture CH_2O–1,2-ethanedithiol (2:1) in the presence of 5 mol % $BF_3\cdot OEt_2$ or BuONa (see Table 1).



n = 1 (**3a**); 2 (**3b**); 3 (**3c**); 4 (**3d**); 5 (**3e**)

Scheme 1. Synthesis of compounds **4**a–**f**.

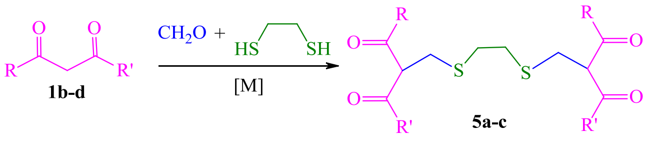
Table 1
The dependence of products **4**a–**f** yield from thiomethylation condition of **1a**[a]

Entry	α,ω-dithiols	Catalyst [M], (mol %)	Reaction duration, (h)	Reaction product	Yield, (%)
1	**3**a	$BF_3\cdot OEt_2$ (5)	6	**4a**	23
2	**3**a	$BF_3\cdot OEt_2$ (5)[b]	6	**4a**	61
3	**3**a	$BF_3\cdot OEt_2$ (5)	6	**4a**	81
4	**3**a	BCl_3 (5)[c]	6	**4a**	76
5	**3**a	$FeCl_3$ (5)	6	**4a**	46
6	**3**a	$FeCl_3\cdot 6H_2O$ (5)	6	**4a**	36
7	**3**a	$CoCl_2\cdot 6H_2O$ (5)	6	**4a**	41
8	**3**a	$NiCl_2\cdot 6H_2O$ (5)[7]	6	**4a**	62
9	**3**a	$CuCl_2\cdot 6H_2O$ (5)	6	**4a**	68
10	**3**a	BuONa (5)	3	**4a**	87
11	**3**a	Al_2O_3/SiO_2[8]	6	**4a**	60
12	**3**a	BuONa (100)	0.5	**4a**	97
13	**3**a	$Ca(OH)_2$ (200)	1	**4a**	30
14	**3**a	NaOH (100)[9]	6	**4a**	64
15	**3b**	$BF_3\cdot OEt_2$ (5)	6	**4b**	80
16	**3c**	$BF_3\cdot OEt_2$ (5)	6	**4**c	81
17	**3d**	$BF_3\cdot OEt_2$ (5)	6	**4d**	87
18	**3e**	$BF_3\cdot OEt_2$ (5)	6	**4e**	85
19	**3f**	$NiCl_2\cdot 6H_2O$ (5)	6	**4f**	68

[a] Reaction conditions: formaldehyde (20 mmol), α,ω-dithiols **3a**–**f** (10 mmol), 2,4-pentanedione **1a** (20 mmol), solvent: $CHCl_3$: C_2H_5OH (1:1 volume), rt, under argon.
[b] The reaction was carried out in CH_2Cl_2.
[c] The reaction was carried out in C_6H_{14}.

Applying this methodology, the thiomethylation of acetylacetone **1**a with other agents (**3a**–**f**) has been performed selectively to obtain high-yield bis[(pentane-2,4-dione-3-yl)methylsulfanyl]alkanes **4a**–**e** and 1,5-bis[(pentane-2,4-dione-3-yl)methylsulfanyl]-3-thiopentane **4f**.

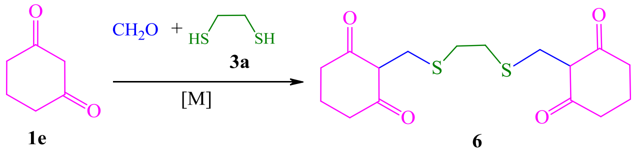
Analogously, MCRs of CH_2O and 1,2-ethandithiol **3a** (5 mol % BuONa) with other aliphatic 1,3-diketones, such as 3,5-heptanedione **1b**, 2,6-dimethyl-3,5-heptanedione **1c**, and 2,2,6,6-tetramethyl-3,5-heptanedione **1d**, leads to 1,2-bis[(1,3-diketone-2yl)methylsulfanyl]ethanes **5a**–**d** (see Scheme 2). Based on the product yield **4a** (87%), **5a** (85%), **5b** (79%) and **5c** (18%) the reactivity of examined aliphatic diketones was specified depending on steric factors and decreased in an order **1a**≥**1b**>**1**c>**1d**.



R = R' = Et (**5a**); *i*-Pr (**5b**); *t*-Bu (**5c**)

Scheme 2. Catalytic thiomethylation of aliphatic 1,3-diketons **1b**–**d**.

Under the above optimized conditions, 1,3-cyclohexanedione **1e** is less active in the reactions with CH_2O and 1,2-ethanedithiol (about 30% conversion). The yield of the target 1,2-bis[(cyclohexane-1,3-dione-3-yl)methylsulfanyl]ethane **6** can be raised to 60% when using a tandem catalyst –10 mol % $NiCl_2\cdot 6H_2O$-hexadecyltrimethylammonium bromide (HDTMAB) or NaOAc-HDTMAB at 70 °C (see Scheme 3, Table 2, entries 9–11).



Scheme 3. Catalytic thiomethylation of cyclohexane-1,3-dione **1e**.

Table 2
Catalyst effect on the yield of **6**[a]

Entry	Catalyst [M], (mol %)	Solvent	Reaction duration, (h)	T	Yield, (%)
1	—	C_2H_5OH	18	70	16
2	$BF_3\cdot OEt_2$ (5)	CH_2Cl_2	18	70	—
3	BuONa (200)	$CHCl_3$: C_2H_5OH[b]	18	70	63
4	$NiCl_2\cdot 6H_2O$ (5)	$CHCl_3$: C_2H_5OH[b]	6	rt	37
5	$NiCl_2\cdot 6H_2O$ (5)	$CHCl_3$: C_2H_5OH[b]	18	70	21
6	NaOAc (10)	C_2H_5OH	6	70	58
7	Al_2O_3/SiO_2 (5)	C_2H_5OH	18	70	5
8	HDTMAB (10)	CH_2Cl_2: H_2O[b]	4	70	46
9	NaOAc+HDTMAB (10)	CH_2Cl_2: H_2O[b]	4	70	60
10	NaOAc+HDTMAB (10)	H_2O	4	70	56
11	$NiCl_2\cdot 6H_2O$+HDTMAB (10)	$CHCl_3$: C_2H_5OH[b]	4	70	60

[a] Reaction conditions: formaldehyde (20 mmol), 1,2-ethanedithiols **3a** (10 mmol), 1,3-cyclohexanedione **1e** (20 mmol), solvent, under argon.
[b] Solvents ratio (volumetric) 1:1.

NMR and X-ray studies of compound **4a** confirmed that the enol tautomer is stable both in solution and the crystalline form. Compound **4a** exists in solution apparently as a keto-enol mixture in 1:29 ratio, respectively that has been determined using ^{1}H NMR integral intensities of characteristic protons in C(O)–CH–C(O) group of keto tautomer (δ_H=3.89 ppm) and in O···H···O moiety of enol tautomer (δ_H=16.74 ppm).[10] It is noteworthy that ^{13}C NMR resonances of the methylene units in both keto and enol forms are coincident (see ^{13}C NMR assignments in Fig. 2). The carbonyl, methyne, and methyl carbon atoms of keto form give appropriate resonances at δ=202.0, 68.2, and 29.3, respectively, while carbonyl atoms and those carbons at the double bond of the enol form give peaks δ=191.8 and 106.2, respectively, and methyl carbon atoms resonate at δ=22.7 ppm. In addition, all the methyl protons of the tautomers are shown to undergo rapid exchange in NMR time scale, so that sharp and intensive ^{1}H signal at δ=2.27 ppm assigned to these protons was observable.