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Application of Reagents Replacing Mercaptan in Organic Synthesis

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With the development of green chemistry as the purpose, the application of the economy easily obtained, odorless, stable a-carboxyl two ketene as an alternative to thiol reagents in organic synthesis is studied. Under mild conditions, the mercaptal / ketone reaction by taking a-carboxyl two ketene as odorless thiol reagents is successfully implemented. The experiment is carried out in acetyl chloride methanol system. First of all, the mercaptal / ketone reaction by substituting the reagents by 3-(1, 3 one or two - 2 exposure subunit)-2, and 4 - acetyl-propionyl for 1, 3-Propylene-dithioacetal is successfully carried out. The experimental results show that the reaction activity of compound 4a is obviously higher than that of compound al, so it is determined that 4a is the best substitute reagent for 1, 3- propyl - two mercaptan. Then, for the analogs of 4a - 1-(1, 3 one or two butylene sulfide 2 subunit) acetone 4b, 4, 4-(two ethylthio / two sulfur)-3-ene-2-butanone 4c and 4d respectively for 1, 2-a mercaptan, mercaptal / ketone reaction reagent replaces ethanethiol and section mercaptan, and the conclusion is that the reaction effect is very good.

1. Introduction

Mercaptan is an important organic synthesis reagent. In mercaptan, S - H key energy is 347.3KJ/mol, much smaller than that of 0-H key energy (462.8KJ/mol), which is easy to generate RS free radical for cracks. The sulfur atom has d3 track. Its valence electron is far from the nucleus, which is less bound by the nuclear force. The degree of polarization is large, and because the space around the atom is large, and space block is small, the electronic enhanced nucleophilicity of RSH is strong, with strong nuclear affinity. These properties of thiols give it a wide range of applications in organic synthesis and biosynthesis. It not only has the reaction of free radical type, such as the addition of RS free radical and alkene and the oxidation of mercaptan, but also takes the nucleophilic reaction (Sala et al., 2016; Haerens et al., 2016). Mercaptal / ketone reaction of carboxylic compounds in organic synthesis, especially in the synthesis of multi step synthetic or natural products, has important and wide application. Because it is not only a method to protect carbon compounds, but also an important intermediate of organic synthesis. Because of the important role of the catalyst in the reaction, the study of the reaction is mainly focused on the development of the catalyst, so as to obtain a mild reaction condition and a high degree of chemical selectivity. A variety of catalysts have been reported, such as $BF_3.ET_2O$, $InCl_3$, $ScCl_3$, LIBr, $H_3PW_{12}O_40$ and other Lewis acids or solid acids. They are used as catalysts, the reaction conditions are mild, the operation is simple and the yield is high. Among them, when we use $ScCl_3$, $InBr_3$, LIBr, $LIBF_4$, Sc $(OTf)_3$, $SOCl_2$-SiO_2 and NBS for catalytic reaction, we have a high degree of chemical selectivity of aldehyde and ketone functional groups.

The studies of mercaptal / ketone reaction mainly focused on the development of catalysts, to obtain the chemical selectivity between good ketone functional groups with mild reaction conditions and high yield. In the exploration of green mercaptal / ketone reaction, in addition to the mercaptal / ketone reaction odorless containing 1, 3-propyl two mercaptan polymer reagent, the other is no solvent, ionic liquids and aqueous phase mercaptal / ketone reaction, still using smelly mercaptan as the raw material. In the process of shrinking the ketene in organic synthesis in the process of application development, we make the application study of the odorless α-carboxyl two sulfur as the alternative thiol reagents of mercaptan in organic synthesis. The purpose is to develop the application of green, chemical and rich carboxyl two ketene in organic synthesis.

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Mercaptal / ketone reaction with odourless α-carboxyl two ketene dithioacetals as thiol substituted reagent is first of all studied.

2. Experimental instruments and reagents

2.1 Experimental instruments

Experimental instruments use NIOVA-500 NMR (Nuclear Magnetic Resonance); Mgana-560 micro infrared spectrometer (KBr disk method); WRS-A digital melting point apparatus (thermometer without correction); PE-2400 automatic elemental analyser (Mlostoń, et al., 2017); HPGC6890/MS5973 mass spectrometer; and commonly used experimental instrument (omitted).

2.2 Experimental reagents

The reagents and raw materials used in the experiments can be seen from Table 1.

Table 1: Reagents and raw materials used in the experiments

Reagent name	Reagent specification	Manufacturer
Anhydrous potassium carbonate	A.R.	Shenyang Xinxi Reagent Factory
Carbon disulfide	A.R.	Tianjin Chemical Reagent Second Factory
Two methyl thalidomide	A.R.	Tianjin Tiantai Fine Chemicals Co., Ltd.
Phthalocyanine acetone	A.R.	Tianjin Tiantai Fine Chemicals Co., Ltd.
Ethyl acetate	A.R.	Tianjin Chemical Reagent First Factory
1,3 one or two bromo propane	A.R.	Shanghai Wulian Chemical Plant
1,2 one or two bromethyl	A.R.	Beijing Chemical Plant
Bromoethane	A.R.	Beijing Chemical Plant
Benzyl chloride	A.R.	Beijing Chemical Plant
Anhydrous methanol	A.R.	Beijing Chemical Plant
Absolute ethanol	A.R.	Beijing Chemical Plant
Dichloromethane	A.R.	Beijing Chemical Plant
Petroleum ether	A.R.	Aladdin
Anhydrous ether	A.R.	Aladdin
Magnesium sulfate anhydrous	A.R.	Aladdin
Benzaldehyde	A.R.	Aladdin
Light base benzaldehyde	A.R.	Sigma—Aldrieh
Heliotropine	A.R.	Sigma—Aldrieh
4-methyl benzaldehyde	A.R.	Sigma—Aldrieh
4-methoxy benzaldehyde	A.R.	Sigma—Aldrieh
4-benzaldehyde	A.R.	Sigma—Aldrieh
4-chloro benzaldehyde	A.R.	Sigma—Aldrieh
4-nitro formaldehyde	A.R.	Sigma—Aldrieh
Furan formaldehyde	A.R.	Beijing Chemical Plant
2-phenyl acetaldehyde	A.R.	Beijing Chemical Plant
N-valeraldehyde	A.R.	Beijing Chemical Plant
2-ketones	A.R.	Bai Lingwei Chemical Technology Co. Ltd.
Acetophenone	C.P.	Bai Lingwei Chemical Technology Co. Ltd.
4-amino Acetophenone	A.R.	Bai Lingwei Chemical Technology Co. Ltd.
4-Acetophenone	A.R.	Bai Lingwei Chemical Technology Co. Ltd.
Two phenyl ketone	A.R.	Bai Lingwei Chemical Technology Co. Ltd.
Amyl ketone	A.R.	Bai Lingwei Chemical Technology Co. Ltd.
cyclohexanone	A.R.	Bai Lingwei Chemical Technology Co. Ltd.
Ethylene chloride	A.R.	Bai Lingwei Chemical Technology Co. Ltd.

3. Ketone/mercaptal reaction with odorless 3-(1,3- two -2- subunit -2,4- pentane Dione thiadiazole) as 1, 3- propyl two mercaptan substitute reagent

3.1 Preparation of α-carboxyl two sulfur ketene 1

Experimental procedure: (take 1a synthesis as an example)
For the 50mL round bottom flask, add anhydrous K_2CO_3 (40mmol, 5.5g), acetyl acetone (20mmol, 2.1mL) and DMF (30mL). At room temperature, stir for 0.5h, and in the ice bath, drop CS_2 (22.0mmol, 1.33mL), and then this solution quickly turned to blood red (Wodrich, et al., 2015). The dropping is furnished after 10min, stir for 1h in the ice bath, then add 1, 3 one or two bromopropane (22.0mmol, 1.68mL) to the three bottle neck one-time. At room temperature, stir for 12h, TLC monitoring substrate disappeared. Pour the reaction solution into water, fully stir and then a large number of white objects precipitate. Then, filter, wash, and dry them to obtain pure 1a3.979, yield of 92% (Amoah and Dieter, 2017).

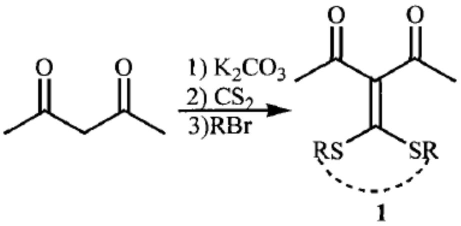

Figure 1: Preparation principle of α-carboxyl two sulfur ketene 1

Table 2: Preparation of α-carboxyl two sulfur ketene 1

Entry	R	Time(h)	Product	Yield (%)
1	(CH2)3	12	1a	92
2	(CH2)2	10	1b	94
3	CH2CH3	12	1c	90
4	CH2Ph	12	1d	95

3.2 ketone/mercaptal reaction between 3- (1,3- two -2- subunit -2,4- pentanedione thiophene) 1a and aldehyde/ketone

Experimental procedure: (take the synthesis of compound 3ea as an example)
Respectively weigh compound 1a for 216mg (l.0mmol) piperonal 2e for l50mg (l.0mmol), add to 50mL round bottom flask, add 5mL methanol and 0.11mL (1.5mmol) acetyl chloride, and stir and heat for reflux. Make TLC monitor until piperonal disappeared, and after cooling, pour the reaction liquid into 100mL water, and extract with 10% $NaHCO_3$ solution (10mLx3) (Noy, et al., 2015). Combine the organic layer, dry it by anhydrous MgS04, column chromatography (eluent ether=50:1), and obtain a white crystalline product 3ae for 204mg, yield of 85%.

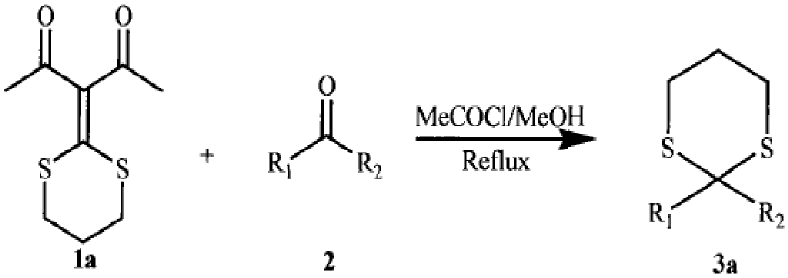

Figure 2: Ketone/mercaptal reaction between 3- (1, 3- two -2- subunit -2, 4- pentanedione thiophene) 1a and aldehyde/ketone

Table 3: Ketone/mercaptal reaction between 3- (1,3- two -2- subunit -2,4- pentanedione thiophene) 1a and aldehyde / ketone

Entry	Subsrtate2					
		R1	R2	Time (h)	Product	Yield (%)
1	2a	Ph	H	6.5	3aa	87
2	2b	4-MePh	H	6.0	3ab	86
3	2c	4-Me0Ph	H	6.0	3ac	87
4	2d	4-OHPh	H	6.0	3ad	83
5	2e	3,4-O2CH2Ph	H	6.0	3ae	85
6	2f	4-ClPh	H	6.0	3af	94
7	2g	4-FPh	H	6.0	3ag	90
8	2h	4-NO2Ph	H	7.0	3ah	97
9	2i	2-Furyl	H	6.5	3ai	61
10	2j	2-ThioPhen	H	5.0	3aj	99
11	2k	PhCH2	H	5.5	3ak	78
12	2l	n-C4H9	H	6.0	3al	88
13	2m	4-H2NPh	Me	8.0	3am	82
14	2n	4-NO2Ph	Me	8.0	3an	88
15	2o	Ph	Me	7.5	3ao	90
16	2p	Ph	Ph	9.0	3ap	92
17	2q	n-C4H9	Me	7.0	3aq	89
18	2r	(CH2)4		7.0	3ar	86

4. Results and discussion

4.1 Optimization of reaction conditions

In CH$_3$OH solvent, when refluxing, MeCoOCl, POCl$_3$, (CH$_3$)$_3$SiCl can well catalyze the mercaptal/ketone reaction of 1a. Under the same condition, we also tried to catalyze the reaction with concentrated HCl, but the reaction time was long. Therefore, the economically cheap MeCOCl is chosen as the catalyst for this reaction. In order to optimize the reaction conditions, a series of experiments have been carried out with 1mmol 1a and 1mmol 2e (Kolodych, et al., 2015). The results are shown in Table 4.

Table 4: Mercaptal/ketone reaction of 1a and 2e

Entry	MeCOCl: 1a (mol: mol)	Solvent	Temperature	Time (h)	Yield (%)
1	1：2	CH3OH	Reflux	19	82
2	1：1	CH3OH	Reflux	12	81
3	3：2	CH3OH	Reflux	6	85
4	2：1	CH3OH	Reflux	4	84
5	3：1	CH3OH	Reflux	2.5	86
6	3：2	CH3OH	r.t	96	87
7	3：2	C2H5OH	Reflux	8	82
8	3：2	THF	Reflux	/	
9	3：2	CH2Cl2	Reflux	/	

From the above experimental results, we know that the amount of MeCOCl and the reaction temperature have an important influence on the rate of the above reactions. The greater the amount of substance in MecOCl is, the higher the reaction temperature will, and the faster the rate of reaction is (Table 4, Entry 1-6). Different reaction media have great influence on 1a mercaptal / ketalization reaction. In CH$_3$OH solvent, mercaptal / ketone reaction can be well conducted, and the product yield is high (Table 4, Entry 6). When using C$_2$H$_5$OH as the reaction solvent, the reaction can occur, but the reaction time is long, and the product the yield is low (Table 4, Entry 7). And in aprotic solvents THF and CH_2Cl_2, the reaction does not occur. Therefore, the optimum reaction conditions for the reaction are: CH_3OH as the solvent, MeCOCl as the catalyst, and molar ratio of 1a, 2e and MeCOCl for 2:2:3, reflux (Das, et al., 2017).

4.2 Ketone/mercaptal reaction between 1a and aldehyde and ketone with different structures

Experiments show that, in the optimal reaction conditions, 1a can have mercaptal / ketone reaction with mercaptal / ketone reaction in different structures, 1, 3-two dithiane derivative is prepared with high yield rate. In the reaction and post-treatment, there was no smell of foul odor. Aldehydes and aliphatic ketones react faster than aryl ketones because of the effects of electrons and steric hindrance. For sterically hindered two benzophenone 2p (Table 3, Entry 16), 2 times the amount of 1a should be used in the reaction, otherwise the reaction is not complete. The reason is that in the reaction, the keto group in the intermediates IV produced by 1a or that in the carbonyl ketone acetyl acetic acid methyl ester generated at last can also have mercaptal / ketone reaction and generate the compound 3as (see figure 3). When 1a reacts with aldehydes, ketones and sterically small aromatic keton, mercaptan generated in the reaction system can be well combined with them, not conducting mercaptal / ketone reaction of IV or acetyl acetate methyl. While reacting with the two benzophenone 2p with the larger steric hindrance, the thiol produced cannot effectively react with Zp, and a part of IV or acetyl acetate methyl have ketone / mercaptal reaction and obtain 3as. In addition, functional groups such as NHZ and OH contained in aldehydes or ketones, which are sensitive to MeCOCl, are not changed in the reaction.

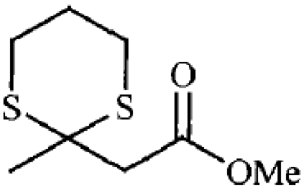

Figure 3: 3as structure drawing

4.3 Mercaptal/ketone reaction mechanism of 1a

In order to study the reaction mechanism, four experiments were carried out. The first one is to add 1mmol compound 1a, 1mmol heliotropine 2e, 1.5mmol MeCOCl and 5mL CH_3OH to the 25mL round bottom flask. Then stir it at room temperature for 4h, and make bisporphyrins reaction. Then, we get 26% 3ae and 5% 1- (1, 3-two dithiane-2- subunit) acetone 4a, and recover 67% 2e and 62% 1a. The second is to make the above reaction with 1mmol 4a instead of 1a. After 2h, the reaction is finished, and then we get 93% 3ea. The third is to make the reflux of 1mmol compound 1a and 1.5mmol MeCOCl in CH_3OH for 6h, and then we get 32% 3as (Matyašovský, et al., 2016). The last one is to add 1mmol heliotropine 2e, 1.5mmolMeCOCl and 5mL CH_3OH to 25mL's round bottom flask. Then, reflux for 2h and conduct TLC monitoring. While we did not observe the formation of other substances, and heliotropine 2e is quantitatively recovered.

From the above four experiments, we can know that: 1) in the reaction, 1a first of all makes deacetylation reaction and generates 4a, and the formation rate of 4a determines the rate of the reaction of ketone / mercaptal; 2) for 1a in the change, its keto group can also make the mercaptal / ketone reaction; 3) in the reaction, it is not to generate the acetal firstly and then make the mercaptal / ketone reaction, but aldehydes or ketones directly has mercaptal / ketone reaction. Therefore, based on the previous work and the above experimental results, the possible reaction mechanism is as follows. First of all, the compound 1a, under the catalysis of HCl produced in the esterification of MeCOCl and CH_3OH, after deacetylation reaction, generates the intermediates 4a. Subsequently, after the addition with hydrogen protons, 4a was converted into I, then I was further attacked by HZO or MeOH, and n and 1n were obtained respectively. They were opened to produce IV, and IV reacted with 2 to form 3a. If the system does not contain 2, then IV has mercaptal / ketone reaction itself and generates 3as.

5. Conclusions

First of all, in the acetyl chloride - methanol system, we successfully carried out without mercaptal/ketone reaction with precursor 1a of the odorless 2- (2 4-, two -1 chloride, 4- diene -3-methylene) -1 and 3- dithiane-2 as the thiol substituted reagent. The success of this reaction fully demonstrates that, under suitable conditions, odourless a-ketene can be used as a thiol substitution reagent to be applied in synthesis. On this basis, through the reagent optimization, we determine odourless, easy to prepare, stable and high activity reagents. In short, in the acetyl chloride methanol system, under reflux conditions, we successfully make mercaptal/ketone reaction of a-sulfur ketene 1a as 1, 3 alternative thiol reagent, and discuss its reaction mechanism. The reaction not only has good universality and high chemical selectivity, but also has no foul smell during the reaction. It is of great importance to the protection of environment and human health. The success of mercaptal / ketone reaction of 1a also fully shows that under appropriate reaction conditions, odorless a-sulfur ketone can replace the smelly mercaptan to be applied in organic synthesis.

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