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Dithiocarbamic acids and thiols as nucleophiles in the Bargellini reaction

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KEYWORDS

Dithiocarbamic acids;
Thioles;
Bargellini reaction.

Abstract Dithiocarbamic acids and thiols are employed in the Bargellini reaction to generate useful intermediates for the synthesis of organic molecules. This is the first time that dithiocarbamic acids are used as nucleophile in this reaction.

1. Introduction

About a century ago, Bargellini reported the condensation of phenols with chloroform and acetone to furnish α-phenoxyisobutyric acids in the presence of sodium hydroxide (Scheme 1) [1]. However, he modified the structure attributed to this condensation, which was suggested by Link a few years earlier [2].

Although initial studies were confined to phenolic substrates, later investigators extended this reaction to aliphatic alcohols by condensation with 1, 1, 1-trichloro-2-methyl-2-propanol, with better yields [3]. Thus, a simple and general methodology for conversion of alcohols to α-alkoxyisobutyric acid systems was developed. Dealkoxylation of these products produced methacrylic acids.

After the initial report, variations in both nucleophiles and ketones have been investigated in the Bargellini reaction. Youseff used phenols as nucleophiles and cyclopentanone as ketone [4]. Grella investigated a wider range of cyclic ketones under Bargellini reaction conditions [5]. As an alternative approach for the synthesis of α-amino acids, Reeve and Corey used potassium amide and sodium azide as nucleophiles, respectively [6,7]. Also, Butcher used aromatic amines and thiophenol as nucleophiles in the Bargellini reaction [8].

By using aminoethanol, the amine functionality serves as a nucleophile and the resultant acid undergoes an intramolecular lactonisation to produce 2-oxomorpholine [9]. An unusual case is also reported, in which the *para*-carbon atom is functioning as a nucleophile in a hindered phenol [10].

2. Results and discussion

The Bargellini reaction offers a multi-component, atom economical synthesis of molecules, with significantly increased complexity, diversity and functionality. In continuation of our interest in finding new and efficient methods for the synthesis of novel dithiocarbamate derivatives [11], herein we describe the utility of dithiocarbamic acids and thiols as nucleophiles in the Bargellini reaction (Scheme 2). Also, it is found that dithiocarbamic acids and thiols react in acceptable yields with three model ketones (acetone, cyclohexanone and cyclopentanone). *This expands the scope of nucleophiles that are known to work in the Bargellini reaction* (Table 1), *although the synthesized compounds extend the scope of this reaction, which can be utilized as initiators, chain transfer agents or terminators for controlled free-radical polymerization* [12]. Improvements have also been found in isolation of the reaction products.

Significantly, we observed that in the reactions of dithiocarbamic acids with acetone and cyclohexanone, the sodium salt of the product precipitated from the reaction mixture, allowing easy isolation of the target molecule at very high purity, without the need for crystallization or chromatography (Table 1, entries 1–10). There are no examples in the literature employing dithiocarbamic acids as nucleophile in the Bargellini reaction. In studying the effect of substituents on the alpha-position of

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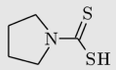
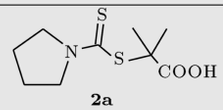
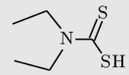
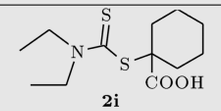
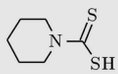
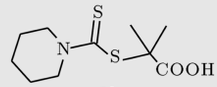
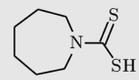
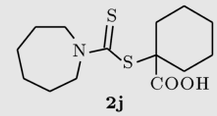
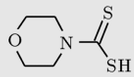
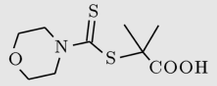
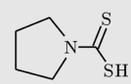
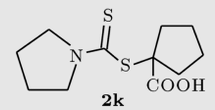
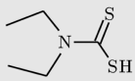
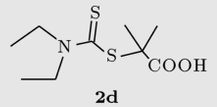
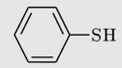
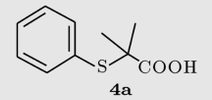
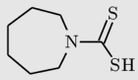
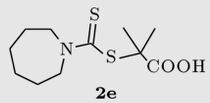
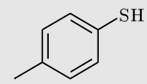
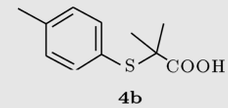
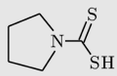
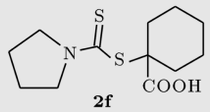
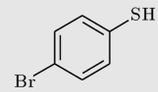
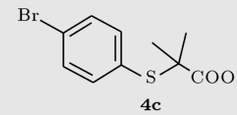
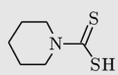
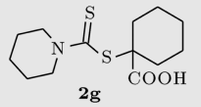
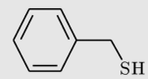
Table 1: Dithiacarbamic acids and thoils as nucleophile in the Bargellini reaction.

Entry	Nucleophile	Keton	Product	Yield %	Entry	Nucleophile	Keton	Product	Yield %
1			 **2a**	85	9			 **2i**	85
2			 **2b**	82	10			 **2j**	75
3			 **2c**	83	11			 **2k**	47
4			 **2d**	87	12			 **4a**	75
5			 **2e**	80	13			 **4b**	78
6			 **2f**	83	14			 **4c**	70
7			 **2g**	81	15			**4d**	68
8			**2h**	77	16			**4e**	82
					17			**4f**	58

the ketones, a series of reactions were done with 2-butanone and 2-methylcyclohexanone under various conditions, but no products were observed in these cases.

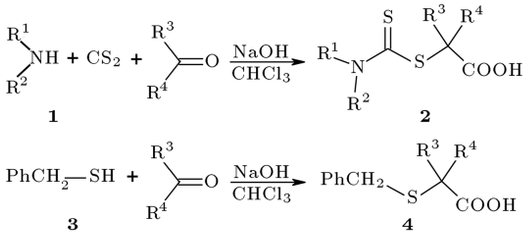
The dithiocarbamic acids that are used in this reaction are synthesized *in situ* by the reaction of secondary amines with carbon disulfide. It is worth mentioning that when dithiocarbamic acids are synthesized with primary amines, and then used as nucleophiles, the desired product was not formed. For example, when 1-butanamine was employed, 1-mercaptocyclohexanecarboxylic acid **5** was formed as a product (Scheme 3).

We further extended the range of novel nucleophiles by reacting aromatic [13] and aliphatic thiols with model ketones. Once again, isolation by precipitation of the sodium salt furnished pure products using minimal purification (Table 1, entries 12–17).

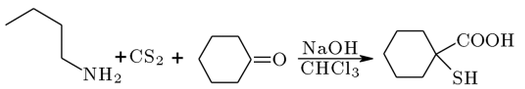
Scheme 1: (i) $CHCl_3$, powdered NaOH, acetone, reflux, 6 h; (ii) HCl.

3. Conclusion

In summary, we have reported a very mild, simple and catalyst-free method for addition of dithiocarbamic acids and thioles to ketones. This process imposes moderate conditions and a simple work-up procedure with high efficiency. To our knowledge, this is the first report of synthesizing this class of compounds by this method.



Scheme 2: Dithiocarbamic acids and thiols as nucleophile in Bargellini reaction.



Scheme 3: The use of dithiocarbamic acids with primary amines in the Bargellini reaction.

4. Experimental section

4.1. General procedure

Preparation of compounds 2*a* − 2*k*: In a 50 mL round-bottom flask, fitted with a magnetic stir-bar in an ice-bath, CS_2 (7.5 mmol) was added to amine (5 mmol) and stirred for 10 min. Then, acetone (10 mL) was added (in the case of compounds 4*a*–4*e*, acetone was added to 5 mmol of thiol). Powdered NaOH (47 mmol) was added in small portions with stirring. The mixture became warm and was cooled to about 35 °C. Then, chloroform (2 mL) was added, within 10 min, while stirring the solution. The reaction mixture was then refluxed for 7 h. The solid precipitated was filtered off and dissolved in water. The solution was extracted with diethyl ether (3 mL × 20 mL) and the aqueous layer was separated. The aqueous layer was cooled and acidified with hydrochloric acid (2 M) to pH 1, and then extracted with EtOAc (40 mL). The EtOAc layer was separated, washed with brine (3 mL × 10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford the desired product as a solid residue.

Preparation of compounds 4*a* − 4*f*: In a 50 mL round-bottom flask, fitted with a magnetic stir-bar in an ice-bath, CS_2 (4.5 mmol) was added to amine (3 mmol) and stirred for 10 min. Then, THF (40 mL) was added and cooled in an ice bath (in the case of compound 4*f* THF was added to 3 mmol of thiol). NaOH powder (15 mmol) and cyclohexanone (or cyclopentanone) (9 mmol) were added. Then, chloroform (2 mL) was added drop wise, the reaction mixture was stirred at 0 °C for 1 h and then stirred at room temperature for 18 h. The solid precipitated was filtered off and dissolved in water. The solution was extracted with diethyl ether (3 mL × 20 mL) and the aqueous layer was separated. The aqueous layer was cooled and acidified with hydrochloric acid (2 M) to pH 1, and then extracted with EtOAc (40 mL). The EtOAc layer was separated, washed with brine (3 mL × 10 mL), dried (Na_2SO_4), filtered and concentrated in vacuo to afford the desired product as a solid residue.

4.2. Selected spectroscopic data

2-Methyl-2-(pyrrolidine-1-carbodithioyl)propanoic acid (2*a*): ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.63 (t, 2H), 3.43 (t, 2H), 1.92 (m, 2H), 1.81 (m, 2H), 1.57 (s, 6H). ^{13}C NMR (125 MHz; $CDCl_3$) δ 189.9, 175.6, 54.2, 54, 50.7, 26.5, 26.2, 24.4. mp 157–159 °C. IR (KBr) (υ_{max}, cm^{-1}): 3500–3000, 1704, 1596, 1514, 1446, 1282, 1225, 1138, 1038.

2-Methyl-2-(morpholine-4-carbodithioyl)propanoic acid (2*c*): ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.9 (br, 4H), 3.59 (t, 4H), 1.58 (s, 6H). ^{13}C NMR (125 MHz; $CDCl_3$) δ 194.8, 177.2, 66.4, 55, 50.3, 26.3.

2-(Diethylcarbamodithioyl)-2-methylpropanoic acid (2*d*): ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.81 (q, 2H), 3.59 (q, 2H), 1.62 (s, 6H), 1.17 (t, 3H), 1.1 (t, 3H). ^{13}C NMR (125 MHz; $CDCl_3$) δ 192.9, 176.6, 54.7, 48.4, 47.3, 26.3, 12.8, 11.8.

2-(Azepane-1-carbodithioyl)-2-methylpropanoic acid (2*e*): ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.5 (br, 1H), 4.1 (t, 2H), 3.8 (t, 2H), 1.8 (m, 4H), 1.7 (s, 6H), 1.6 (m, 4H). ^{13}C NMR (125 MHz; $CDCl_3$) δ 193.4, 179.4, 55, 54.9, 53.5, 27.9, 27.1, 27, 26.6, 26.4. mp 161.5–163.5 °C.

1-(Pyrrolidine-1-carbodithioyl)cyclohexanecarboxylic acid (2*f*): ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.7 (br, 1H), 3.82 (t, 2H), 3.64 (t, 2H), 2.05 (m, 2H), 1.94 (m, 2H), 1.75–1.6 (m, 8H), 1.4–1.25 (m, 2H). ^{13}C NMR (125 MHz; $CDCl_3$) δ 189.7, 179, 60.3, 54.5, 51.4, 33.8, 26.7, 25.4, 24.7, 22.3. mp = 150–152 °C.

1-(Piperidine-1-carbodithioyl)cyclohexanecarboxylic acid (2*g*): ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.4 (br, 1H), 4.1 (br, 4H), 2.4 (dd, 2H), 2.1 (m, 2H), 1.7–1.6 (m, 11H), 1.37 (m, 1H). ^{13}C NMR (125 MHz; $CDCl_3$) δ 192.4, 179.8, 60.6, 51.9, 34, 25.8, 24.5, 22.8.

1-(Diethylcarbamodithioyl)cyclohexanecarboxylic acid (2*i*): ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.7 (br, 1H), 3.93 (m, 2H), 3.76 (m, 2H), 2.36 (m, 2H), 2.17 (m, 2H), 1.8–1.55 (m, 6H), 1.4–1.2 (m, 6H). ^{13}C NMR (125 MHz; $CDCl_3$) δ 192.3, 179.1, 60.5, 49, 48, 33.9, 25.8, 22.7, 13, 12.

1-(Pyrrolidine-1-thioyl)cyclopentanecarboxylic acid (2*k*): ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.1 (br, 1H), 4.16 (br, 2H), 3.85 (br, 2H), 2.61 (m, 2H), 2.24 (m, 2H), 1.8 (m, 4H), 1.69 (m, 6H). ^{13}C NMR (125 MHz; $CDCl_3$) δ 194, 179, 64.5, 52, 38.4, 31.9, 25.9, 24.7, 23, 21.

2-Methyl-2-(phenylthio)propanoic acid (4*a*): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52–7.26 (m, 5H), 1.45 (s, 6H). ^{13}C NMR (125 MHz; $CDCl_3$) δ 176.5, 136.96, 132, 129.3, 128.8, 51.2, 26.4.

2-(4-Bromophenylthio)-2-methylpropanoic acid (4*c*): ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.14 (br, 1H), 7.48 (d, 2H), 7.39 (d, 2H), 1.52 (s, 6H). ^{13}C NMR (125 MHz; $CDCl_3$) δ 180.2, 138.6, 132, 130.7, 124.9, 51.1, 25.8.

2-Methyl-2-(naphthalen-3-ylthio) propanoic acid (4*e*): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (s, 1H) 7.85–7.78 (m, 3H), 7.59–7.49 (m, 3H), 1.58 (s, 6H). ^{13}C NMR (125 MHz; $CDCl_3$) δ 180.4, 137.3, 133.8, 133.7, 133.4, 128.9, 128.6, 128.4, 128, 127.4, 126.8, 51.2, 26.

1-(Naphthalen-3-ylthio)cyclohexanecarboxylic acid (4*f*): ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.6 (br, 1H), 8.1 (s, 1H), 7.85–7.78 (m, 3H), 7.61 (d, 1H), 7.53 (m, 2H), 2.2 (m, 2H), 1.8–1.7 (m, 5H), 1.4 (m, 3H). ^{13}C NMR (125 MHz; $CDCl_3$) δ 179, 173, 143, 137, 133, 128.5, 128, 127.4, 126.8, 56, 37, 27.4, 25.6.

Acknowledgment

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