Novel One-Pot, Four-Component Synthesis of 3-Alkyldithiocarbonyl-oxazolidines from Aminoethanols, Ketones, Carbon Disulfide, and Halides

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Abstract: A novel one-pot, four-component synthesis of 3-alkyldithiocarbonyloxazolidine derivatives from aminoethanols, ketones, carbon disulfide, and halides was developed. A series of substituted 3-alkyldithiocarbonyloxazolidine derivatives were synthesized in excellent yields utilizing this newly developed method.

Key words: four-component synthesis, aminoethanol, 3-alkyldithiocarbonyloxazolidines, dithiocarbamate, anhydrous K_3PO_4

Dithiocarbamates are important sulfur-containing compounds, which possess broad applications in organic and medicinal chemistry. As protecting groups[1] and synthetic precursors,[2] they have been widely used in the synthesis of trifluoromethylamines,[3] thioureas,[4] aminobenzimidazoles,[5] isothiocyanates,[6] alkoxyamines,[7] and total synthesis of (–)aphanorphine.[8] On the other hand, dithiocarbamates are of growing interest due to their biological potencies,[9] such as antihistaminic,[10] antibacterial,[11] and anticancer activties.[12] Owing to their strong metal-binding capacity, they can also act as enzyme inhibitors, such as indoleamine 2,3-dioxygenase (IDO), which plays an important role in tumor growth.[13]

In view of their potential chemical and biological values, much effort has been devoted to the development of efficient methods for the synthesis of this type of compounds. Several available methodologies are: (a) utilizing thiophosgene,[14a] chlorothioformates,[14b] and isothiocyanates[14b] as starting materials; (b) reaction of amines with carbon disulfide and alkyl halides in the presence of strong bases such as KOH,[15a,b] NaOH[15b] or Cs_2CO_3 and TBAI;[16] (c) reaction of amines with carbon disulfide and active methylene compounds in the presence of CBr_4.[17] Although these methods provided dithiocarbamates successfully, they still suffered from serious drawbacks, such as toxic and unavailable reagents,[14a,b] limited scope,[17] and especially the use of strong bases,[15a,b] which led to the difficult preparation of base-sensitive compounds. Recently, Saidi and his colleagues reported a catalyst-free and solvent-free synthesis of dithiocarbamates from amines, carbon disulfide, and alkyl halides[18a] or α,β-unsaturated compounds[18b,c] or epoxides.[18d] Undoubtedly, from the organic synthesis point of view, the method was very admirable. However, the method lost its generality and efficiency in generating highly functionalized molecules with complexity and diversity using four or more components in one-pot reaction.

During our research aimed at discovering dithiocarbamates as novel anticancer drugs, we developed a very useful methodology utilizing anhydrous K_3PO_4 as promoter,[19] and obtained two antitumor lead compounds **1** and **2** (Figure 1).[12c,20,21] As a continuation of this work, and in connection with oxazolidines exhibiting unique roles in some bioactive molecules,[22] a new class of dithiocarbamic acid esters with oxazolidine moiety **3a–n** was designed (Figure 1). However, they were difficult to synthesize directly from the one-pot reaction of oxazolidines, carbon disulfide, and electrophilic reagents because most of the oxazolidine derivatives are not commercially available. In the present work, we wish to report a novel anhydrous K_3PO_4-promoted one-pot, four-component synthesis of 3-alkyldithiocarbonyloxazolidine derivatives from aminoethanols, ketones, carbon disulfide, and halides (Scheme 1). In this strategy, the oxazolidine intermediates, which are formed from different aminoethanols and ketones, are not isolated from the reaction system, but directly reacted with carbon disulfide and alkyl halides. Therefore, 3-alkyldithiocarbonyloxazolidine derivatives could be directly prepared from aminoethanols.

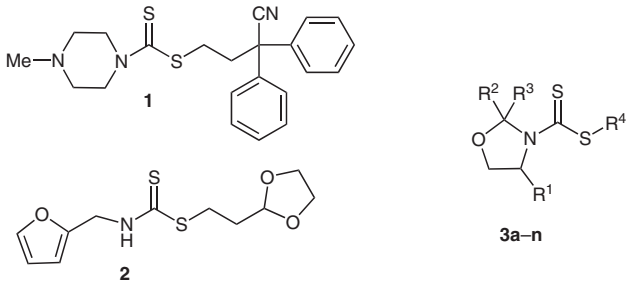
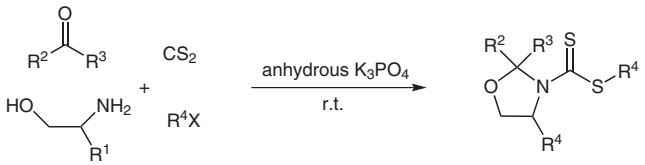


Figure 1 The structures of compound **1**, **2**, and **3a–n**



Scheme 1 The four-component synthesis of **3a–n**

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Table 1 Four-Component Reaction for the Synthesis of **3a–n** in the Presence of Anhydrous K_3PO_4[23]

Entry[a,b]	R^1	R^2	R^3	R^4	Product[24]	Mp (°C)	Yield (%)[c]
1	H	Me	Me	Me	**3a**	60–62	87
2	H	Me	Me	Et	**3b**	oil	89
3	H	Me	Me	*i*-Pr	**3c**	oil	86
4	H	Me	Me	cyclopentyl	**3d**	46–48	82
5	H	Me	Me	$PhCH_2CH_2$	**3e**	42	84
6	H	Me	Me	$(Ph)_2(CN)CCH_2CH_2$	**3f**	104–106	80
7	H	Me	Me	$CNCH_2CH_2$	**3g**	36	81
8	H	Me	Me	EtO_2CCH_2	**3h**	oil	84
9	Me	Me	Me	$PhCH_2CH_2$	**3i**	54–56	83
10	H	$-(CH_2)_5-$		$PhCH_2CH_2$	**3j**	oil	82
11	H	$-(CH_2)_6-$		Et	**3k**	79–80	81
12	H	Me	Et	$PhCH_2CH_2$	**3l**	oil	81
13	Me_2CHCH_2	Me	Me	Et	**3m**	oil	81
14	Bn	Me	Me	Et	**3n**	oil	84

[a] Products have been characterized by ^1H NMR, MS, and elemental analyses.
[b] For entries 1–9, 13 and 14 excess acetone was used as solvent; for entries 10–12 DMF was selected as the solvent; the molar ratios of aminoethanol and ketones are 1:1.1; 4 Å MS were used as additive; other conditions keep unchanged.
[c] Isolated yields.

Initially, the four-component reaction of aminoethanol, acetone, carbon disulfide, and iodomethane in the presence of anhydrous K_3PO_4 was chosen to investigate, and the desired product **3a** was obtained in an excellent yield. We then used this reaction as a model to optimize the reaction conditions, and the result was evaluated qualitatively by TLC. Different reaction temperatures (0 °C, r.t., reflux) and molar ratios of anhydrous K_3PO_4 and reagents were examined. The best result was achieved by carrying out the reaction with 1:2:1:2 molar ratios of aminoethanol, carbon disulfide, iodomethane, and anhydrous K_3PO_4 at room temperature for three hours. The desired product, 2,2-dimethyl-3-(methyldithiocarbonyl)oxazolidine **3a**, was thus obtained in 87% yield (entry 1, Table 1).

With the optimized conditions in hand, we then examined the scope and limitation of this method. Various alkyl halides containing different functional groups, such as nitrile and ester, were tested. All the reactions proceeded smoothly to give the corresponding products in high yields (entries 2–6, Table 1). The alkyl bromides participated in the reactions affording corresponding compounds **3b–f** in 80–89% yields within three hours. β-Bromopropionitrile and ethyl α-chloroacetate were used as alkylating agents to give products **3g** in 81% and **3h** in 84% yields, respectively (entries 7 and 8). Apparently, the functional groups in halides did not have any effect on the reaction due to the very mild reaction conditions. The substituted aminoethanols and other ketones were subsequently examined. Consistent with the previous studies, replacing aminoethanol with 2-methylaminoethanol, 2-isobutylaminoethanol, or 2-benzylaminoethanol, the reaction performed smoothly and afforded desired products **3i**,**m**,**n** in 83%, 81%, and 84% yields, respectively (entries 9, 13, and 14). When other ketones instead of acetone were used, satisfactory results were also obtained (entries 10–12). Therefore, the present protocol is tolerable to the structural variations of the aminoethanol, ketone, and alkyl halide components.

Anhydrous K_3PO_4 plays an important role in this reaction. Though its role is not completely clear, we consider that anhydrous K_3PO_4 may have three actions, namely base, dehydrating agent, and phase-transfer catalyst.[23]

In conclusion, we have developed a novel one-pot, four-component synthesis of 3-alkyldithiocarbonyl-oxazolidines from aminoethanols, ketones, carbon disulfide, and alkyl halides. Various substituted 3-alkyl-dithiocarbonyloxazolidine derivatives were synthesized in excellent yields by using this method. The evaluation of these compounds for their anticancer activity and further extension of this methodology are in progress and will be reported in due course.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(24) **Typical Procedure for the Synthesis of Compounds 3**
To a solution of aminoethanol (2 mmol) in acetone (10 mL) was added anhyd K_3PO_4 (4 mmol), and the reaction mixture was stirred at r.t. for 30 min. CS_2 (4 mmol) was then added dropwise. The reaction mixture was stirred for an additional 20 min, and halide (2 mmol) was then added. Stirring was continued at r.t. until the reaction was completed (monitored by TLC). The precipitate was filtered and washed with acetone. The solvent was evaporated under reduced pressure, and the residue was purified by chromatography on a silica gel column (PE–EtOAc) to give the desired compounds **3**.
Selected Data for Compound 3f
White solid; mp 104–106 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.83 (s, 6 H), 2.81 (t, *J* = 7.8 Hz, 2 H), 3.30 (t, *J* = 8.1 Hz, 2 H), 3.82 (t, *J* = 6.3 Hz, 2 H), 4.06 (t, *J* = 6.3 Hz, 2 H), 7.26–7.49 (m, 10 H). MS (EI, 70 eV): *m/z* (%) = 396 (6) [M]$^+$, 204 (7), 193 (7), 177 (55), 165 (15), 144 (57), 118 (25), 86 (100). Anal. Calcd for $C_{23}H_{26}N_2OS_2$: C, 66.63; H, 6.10; N, 7.06. Found: C, 66.71; H, 6.10; N, 7.03.
Selected Data for Compound 3h
Light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.30 (t, *J* = 7.2 Hz, 3 H), 1.83 (s, 6 H), 3.93 (t, *J* = 6.3 Hz, 2 H), 4.10 (t, *J* = 6.3 Hz, 2 H), 4.13 (s 2 H), 4.23 (q, *J* = 7.2 Hz, 2 H). Anal. Calcd for $C_{10}H_{17}NO_3S_2$: C, 45.60; H, 6.51; N, 5.32. Found: C, 45.45; H, 6.57; N, 5.36.