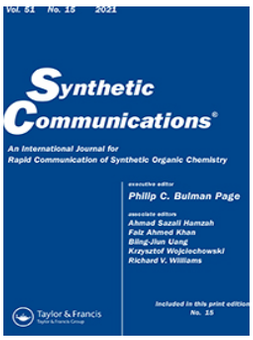

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# A convenient way for alkylation of amines using xanthate esters

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# A convenient way for alkylation of amines using xanthate esters

Kodipura P. Sukrutha[a], Toreshettahally R. Swaroop[b], Ramesh Preetham[a], Neratur K. Lokanath[c], Kanchugarakoppal S. Rangappa[d], and Maralinganadoddi P. Sadashiva[a]

[a]DOS in Chemistry, University of Mysore, Mysuru, India; [b]DOS in Organic Chemistry, University of Mysore, Mysuru, India; [c]DOS in Physics, University of Mysore, Mysuru, India; [d]Institution of Excellence, University of Mysore, Mysuru, India

**ABSTRACT**

*N*-alkylation of amines by the reaction with xanthate esters in the presence of acetic acid catalyst in ethanol is reported. Short reaction time, high yield, general applicability and environmentally benign nature are the noteworthy features of our protocol. The probable mechanism for the formation *N*-alkylation of amines is proposed.

**GRAPHICAL ABSTRACT**


**ARTICLE HISTORY**
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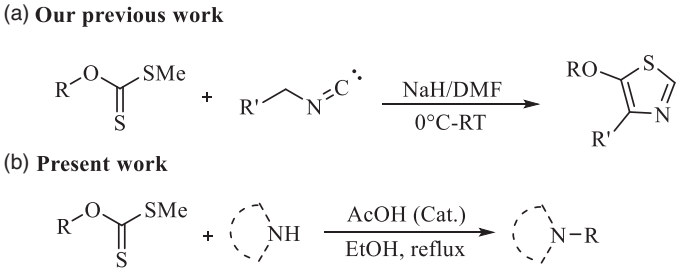
**KEYWORDS**
Acetic acid; amines; ethanol; N-alkylation; xanthate esters

## Introduction

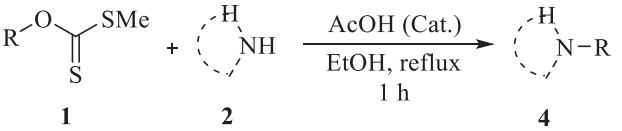
Heterocyclic compounds present in many drugs and natural products.[1] During synthetic transformations, *N*-alkylations are key steps in multistep synthetic sequences.[2] They are generally achieved by treatment of nitrogen compounds with suitable bases like potassium carbonate,[3] sodium hydride,[4] triethylamine,[5] *n*-butyl lithium[6] and CsF/Celite[7] followed by treatment with alkylating agents are traditional methods. The other alkylating methods are super base-catalyzed Michael addition of $\alpha,\beta$-unsaturated compounds,[8] *N*-allylic alkylation with allyl esters,[9] hydroamination with alkenes,[10] transition metal-catalyzed cross-coupling with boronic acid[11] and bismuth,[12] carbene insertion into the N – H bonds with methyl phenyldiazoacetate,[13] alkylation with alcohols,[14] ketones[15] and alkoxides[16] and reductive aminations of carbonyl compounds.[17] These reactions are carried out in various solvents such as acetone,

**CONTACT** Toreshettahally R. Swaroop swarooptr@gmail.com DOS in Organic Chemistry, University of Mysore, Mysuru, Karnataka, India; Kanchugarakoppal S. Rangappa rangappaks@gmail.com Institution of Excellence, University of Mysore, Mysuru, Karnataka, India; Maralinganadoddi P. Sadashiva mpsadashiva@gmail.com DOS in Chemistry, University of Mysore, Mysuru, Karnataka, India.
Dedicated to Prof. C. N. R. Rao on his 86th birthday.

Supplemental data for this article can be accessed on the publisher's website.




**Scheme 1.** Our previous and present work



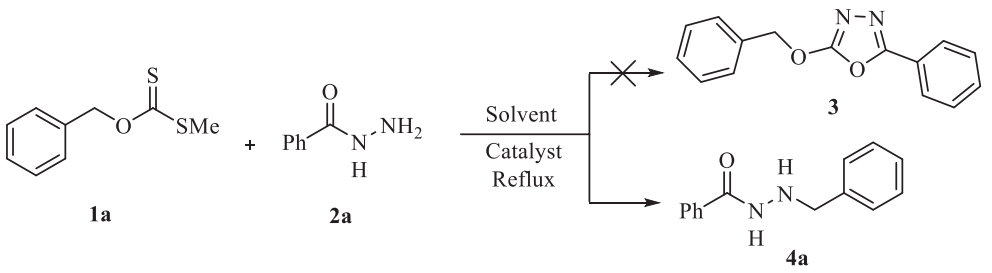

**Scheme 2.** *N*-Alkylation of amines

DMSO,[18] DMF,[19] THF,[20] and HMPT,[21] etc. Besides, *N*-alkylations can be accomplished using phase-transfer catalysts such as *tetra*-butylammonium bromide[22] and crown ether.[23]

Various alkylating agents mentioned above are expensive and less stable except alcohols. Notably, benzyl halides are lacrimetric in nature. The aforementioned methods suffer from limitations such as low yields, harsh reaction conditions, use of toxic solvents or catalysts. Hence, the development of environmentally benign method for *N*-alkylation of heterocyclic compounds is in demand. Recently, in continuation of our efforts in synthetic organic chemistry,[24] we have published cyclization of active methylene isocyanides with xanthate esters for the synthesis of thiazoles (Scheme 1a).[24d] In extension, we aimed to synthesize oxazole **3** from xanthate ester **1a** and benzohydrazide **1b** (Scheme 2). Unexpectedly, we obtained *N*'-benzylbenzohydrazide **4a** (Scheme 2). Later, a generalized *N*-alkylation methodology by using xanthate esters is presented in this article (Scheme 1b).

## Results and discussion

We started optimization of reaction condition for the synthesis of 2-(benzyloxy)-5-phenyl-1,3,4-oxadiazole **3** by selecting the reaction between *O*-benzyl *S*-methyl carbonodithioate **1a** and benzohydrazide **2a** in the presence of acid/base catalyst in a refluxing solvent. But analysis of spectral data indicated the unexpected formation of *N*'-benzylbenzohydrazide **4a** in 40% yield in DMSO solvent and *p*-toluenesulfonic acid catalyst (entry1, Table 1). To improve yield, we started varying solvent. Thus, in DMF and EtOH, the unexpected product **4a** was obtained in 25% and 50% yield respectively (entries 2 and 3, Table 1). On changing the catalyst to AcOH, the yield of **4a** was increased to 85% (entry 4, Table 1). Trifluroacetic acid did not improve the yield (entry 5, Table 1). On the other hand basic catalysts like DBU, trimethylamine and potassium carbonate in varying solvent did not improved the yield of **4a** (entries 6–10, Table 1).




With the optimized reaction condition in hand, we extended our work to explore the generality of the reaction[25] (entry 1, Table 2). Thus, *O*-butyl *S*-methyl carbonodithioate **1b** butylated primary amine benzohydrazide **2a** to produce *N*'-butylbenzohydrazide **4b** in 80% yield (entry 2, Table 2). *O*-Benzyl *S*-methyl carbonodithioate **1c**, *S*-methyl *O*-(2-methylbenzyl) carbonodithioate **1d**, *O*-(3-methoxybenzyl) *S*-methyl carbonodithioate **1e** alkylated aromatic amine benzotriazole **2c** to yield respective products **4c-e** in 78–82% yield (entries 3–5, Table 2). A secondary amine such as morpholine **2d** was benzylated by **1a** to form 4-benzylmorpholine **4f** in 80% yield (entry 6, Table 2). Later, binucleophilic amine piperazine **2d**, was benzylated by **1a** to afford benzylpiperazine **4 g** in 78% yield (entry 7, Table 2). Interestingly, *tert*-butyl piperazine-1-carboxylate **2e** was monoalkylated by **1a** under acidic catalyst acetic acid to furnish *tert*-butyl 4-benzylpiperazine-1-carboxylate **4h** in 76% yield (entry 8, Table 2). Unfortunately, aryl amine such as aniline (**2f)** and secondary sterically hindered diphenylamine **2g** did not furnish any benzylated product **(4i** and **4j)** respectively (entries 9 and 10, Table 2). Finally, benzylamine **2h** on reaction with **1a** under optimized reaction conditions yielded, *O*-benzyl benzylcarbamothioate **4k** in 75% yield (entry 11, Table 2). The structure of One of the *N*-alkylated products, **4a** was confirmed by X-ray crystallography.[26] Notably, only alkylated amine **4b** exists as a rotamer, which was confirmed in NMR (Figure 1).

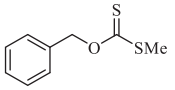
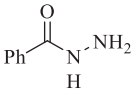
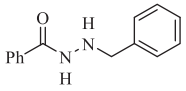
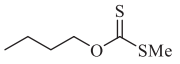
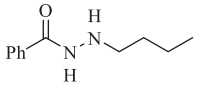
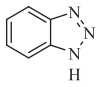
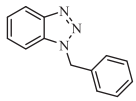
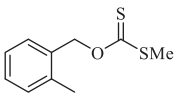
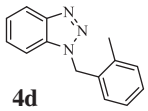
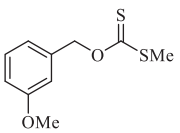
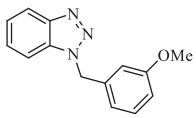
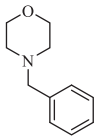
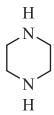
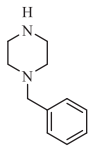
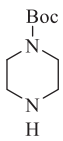
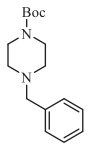
The required xanthate esters were prepared according to our reported protocol.[24h] The probable mechanism for the formation of products is given in Scheme 3. It involves protonation of thiocarbonyl of xanthate ester **1** from acetic acid, followed by nucleophilic attack of amine on **5** resulted in the formation of *N*-alkylated products **4** and intermediate **6**. This is degraded into methanethiol and carbon oxide sulfide.

**Table 1.** Optimization of reaction conditions.

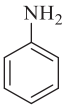
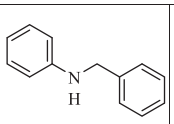
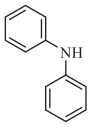
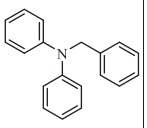
| Entry | Solvent | Catalyst | % Yield |
|---|---|---|---|
| 1 | DMSO | *p*-TSA | 40 |
| 2 | DMF | *p*-TSA | 25 |
| 3 | EtOH | *p*-TSA | 50 |
| 4 | EtOH | AcOH | 85 |
| 5 | EtOH | TFA | 60 |
| 6 | EtOH | DBU | 35 |
| 7 | EtOH | triethylamine | 35 |
| 8 | EtOH | $K_2CO_3$ | 0 |
| 9 | Acetonitrile | DBU | 15 |
| 10 | THF | DBU | 15 |

Reaction conditions: **1a** (5 mmol), **2a** (5 mmol), catalyst (0.05 mmol), solvent (5 mL), 1 h.

**Table 2.** Substrates and products of *N*-alkylation.

| Entry | 1 | 2 | 4 | % Yield |
|---|---|---|---|---|
| 1 |  **1a** |  **2a** |  **4a** | 85 |
| 2 |  **1b** | **2a** |  **4b** | 80 |
| 3 | **1a** |  **2b** |  **4c** | 78 |
| 4 |  **1c** | **2b** |  **4d** | 81 |
| 5 |  **1d** | **2b** |  **4e** | 82 |
| 6 | **1a** |  **2c** |  **4f** | 80 |
| 7 | **1a** |  **2d** |  **4g** | 78 |
| 8 | **1a** |  **2e** |  **4h** | 76 |

(*continued*)

| | | | | |
|---|---|---|---|---|
| 9 | **1a** |  **2f** |  **4i** | 0 |
| 10 | **1a** |  **2g** |  **4j** | 0 |

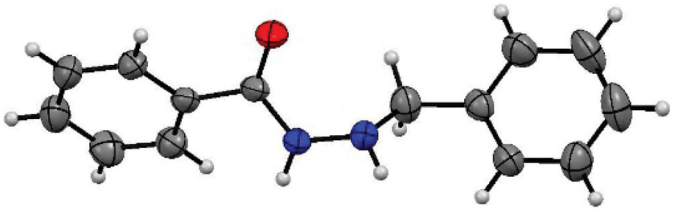
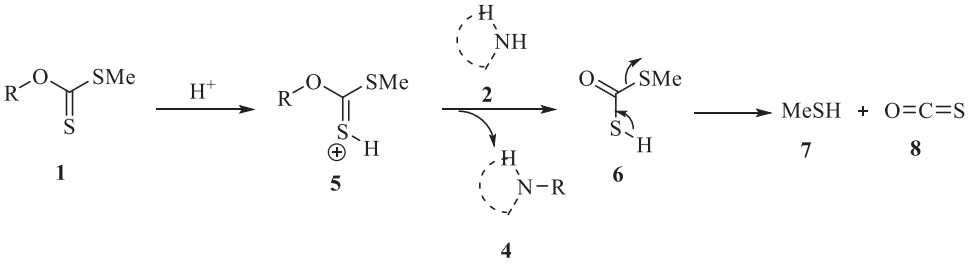


**Figure 1.** ORTEP diagram of **4a**.




**Scheme 3.** The probable mechanism for the formation of products

In conclusion, we have reported a convenient method for the *N*-alkylation of primary amine (benzohydrazide), secondary aromatic heterocyclic amines and secondary alicyclic amines with diverse xanthate esters in the presence of acetic acid in ethanol solvent. Reactions were rapid, eco-friendly and high yielding and overcomes most of the limitations of earlier reported protocols. This novel method is cost effective compared to some of other alkylating reagents and could serve as ideal alkylating reagent in future research.

## Experimental

### *Materials and methods*

All reagents and solvents were purchased from commercial suppliers and used as such. Melting points were determined with a SELACO melting-point apparatus and are uncorrected. All the reactions were monitored by TLC using commercially available

precoated plates (MERCK 60F254, 0.25 mm thickness) and visualized under UV light. $^{1}H$ and $^{13}C$ NMR spectra were obtained with an AGILENT NMR spectrometer having the frequency of 400 MHz. Chemical shift ($\delta$) are given in ppm using $CDCl_3$ and DMSO solvent as reference relative to TMS, coupling constant ($J$) values are given in Hz. Mass spectral analysis was performed with a Water-Synapt G2 mass spectrometer. The single-crystal X-ray diffraction data of the compound was generated with a Rigoku SMART Lab model, Japan, using a Cu source at r.t. with the monochrome beam method. The structure was established by full matrix least square methods using SHELKS program.

### *General procedure for the alkylation of amines 2 from xanthate esters 1*

To a solution of xanthate ester **1** (2 mmol) and amine **2** (2 mmol) in ethanol (5 mL), add (0.2 mmol) glacial acetic acid and reflux the reaction contents for 1 h. The progress of the reaction was monitored by thin layer chromatography (TLC). After the completion of the reaction, ethanol was removed under reduced pressure and water (25 mL) was added. Extract the product with ethyl acetate (25 mL × 2), dry with anhydrous sodium sulfate and concentrate the ethyl acetate later under reduced pressure. Crude products were purified by column chromatography using hexane: ethyl acetate mixture (1:20).

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## ORCID

Kanchugarakoppal S. Rangappa http://orcid.org/0000-0003-0572-6305

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[26] CCDC 2009756 contains the supplementary crystallographic data for compound **4d**. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/getstructures.