DUAL ROLE OF ALKYNYL BROMIDES IN ONE-STEP SYNTHESIS OF BROMO-SUBSTITUTED ALKYNYL SULFIDES

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GRAPHICAL ABSTRACT

Abstract An atom-economical and environmentally friendly method for synthesis of bromo-substituted alkynyl sulfides has been developed. In the absence of any additive, alkynyl bromides could react with tetrahydrothiophene to give bromo-substituted alkynyl sulfides in moderate to perfect yields.

Keywords Additive-free; alkynyl bromide; bromo-substituted alkynyl sulfides; catalyst-free; tetrahydrothiophene

INTRODUCTION

Alkynyl halides, as highly versatile synthons in organic synthesis, have been well understood.[1] Especially when employed as a source of acetylide to synthesize various alkynes, alkynyl halides have been studied extensively.[3] However, when serving as a source of both halogen and alkynyl in the same transformation, alkynyl halides have attracted much less attention.[3–6] Trofimov and coworkers first studied the dual role of alkynyl halides in one-step synthesis of alkynyl epoxides.[3] Other researchers reported that alkynyl halides reacted with arynes to synthesize (alkynyl)-bromoarenes.[4] This method was then extended to three-component coupling reaction and led to the direct construction of alkynyl functionalized bromarenes.[5] Li and coworkers developed palladium-catalyzed direct bromination of C–C

Received March 11, 2014.

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triple bonds or C–C double bonds to synthesize conjugated cis-bromo alkenynes or 7-alkynyl norbornanes and cyclobutenyl halides. These methods represent the importance of atom-economical and environmentally friendly reactions for synthetic chemistry. Therefore, the importance of research into the dual role of alkynyl halides is evident.

Alkynyl sulfides are very important intermediates in organic synthesis and can be used as versatile building blocks for a variety of chemical purposes. Therefore, many efficient methods have been developed for their synthesis. The common methods are based on the transition-metal-catalyzed cross-coupling reaction between alkynyl bromide or terminal alkynes with phenylsulfuryl halides or dialkyl disulfides. It is worth pointing out that use of transition metals has some inherent drawbacks, such as cost and toxicity, though they are a powerful means of effecting organic reactions. Alternative approaches are based on the nucleophilic substitution reaction of lithium acetylide to sulfur-containing compounds under extremely vigorous conditions that do not tolerate many functional groups, thus limiting the synthetic application of these approaches. However, low efficiency of the reaction is a major drawback. Recently, Frei and Waser successfully developed a highly chemoselective and practical thio-alkynylation reaction utilizing the hypervalent iodine alkyne transfer reagent triisopropylsilyl (TIPS) ethynyl benziodoxolone, but the difficult accessibility of alkynylation reagents limited the practical application of this method. Nevertheless, the development of efficient, practical, and atom-economical procedures for the synthesis of alkynyl sulfides is a significantly bigger challenge.

Recently, we reported that alkynyl bromides reacted with tetrahydrofuran (THF) for synthesis of 2-alkynyl tetrahydrofuran derivatives. When THF was replaced by tetrahydrothiophene (THT), we found an interesting transformation: phenylethynyl bromide, in the presence of NaF, reacted with THT to afford 82% of (4-bromobutyl)(alkynyl)sulfide, and no corresponding 2-alkynyl tetrahydrothiophene was observed. Apparently, the phenylethynyl bromide, which served as a source of alkynyl group and bromine, led to the direct construction of bromo-substituted alkynyl sulfide. Such reaction has been deemed to be among the most “aspirational” reactions as yet underdeveloped in key green chemistry research areas favored by the pharmaceutical industry. Herein, we described our preliminary results for the synthesis of bromo-substituted alkynyl sulfides.

RESULTS AND DISCUSSION

Initially, the reaction of phenylethynyl bromide (1a) with THT was selected for optimization of reaction conditions, and the results are summarized in Table 1. At the beginning of our investigation, a variety of bases such as NaF, NaO-t-Bu, and Cs2CO3 and no base were screened (entries 1–4). We were surprised to find that the yield of the desired product was best without any base. Subsequently, the equivalent amount of THT was screened in toluene and dimethylformamide (DMF; entries 5 and 6). The results showed the reaction is infeasible in the equivalent amount of THT. Finally, the volume of THT and the reaction temperature were evaluated, and the best result was obtained at 120 °C in 4 mL THT (entries 7–10). Therefore,
the optimized reaction conditions were as follows: 1a (0.30 mmol), in THT (4 mL) at 120°C.

With the optimal reaction conditions in hand, the reaction of various alkynyl bromides with THT were investigated, and the results are summarized in Table 2. In the absence of additives, the reaction has very good functional group tolerance on substrates. Arylethynylbromides bearing electron-withdrawing groups such as F, Cl, Br, CN, NO2, CH3CO, and CH3OCO afforded the corresponding bromo-substituted alkynyl sulfides in good to perfect yields. For example, products 2d and 2i bearing 4-chlorophenyl or 4-nitrophenyl group were afforded in 95% and 91% yields, respectively. However, arylethynylbromides bearing electron-donating groups such as OMe, CH3, n-C3H7, and n-C5H11 should extended the reaction time (48 h) and afforded the corresponding bromo-substituted alkynyl sulfides in good yields. For example, products 2m and 2n bearing 4-methoxylphenyl or 4-methyl-phenyl group were only afforded in 63% and 73% yields, respectively. These reaction results are attributed to the electron-donating groups on the aromatic ring, increasing the electronic cloud density of the acetylenic bond, which makes nucleophilic addition reaction relatively inert. Furthermore, 4-(bromoethynyl) biphenyl (1q) and 1-(bromoethynyl)naphthalene (1r) could efficiently react with THT to afford the corresponding product in 92% and 73% yields. Importantly, heterocyclic 2-((4-bromobutylthio)ethynyl)thiophene (2s) was obtained in 75% yield, and 1-((4-bromobutylthio)ethynyl)cyclohexanol (2t) bearing a hydroxyl was given in 43% yield.

To probe the reaction mechanism, a crossover experiment was conducted under standard condition with a 1:1 mixture of 1u and 1m (Scheme 1). The crossover products were detected by either gas chromatography–mass spectrometry (GC-MS) or 1H NMR, and (4-halobutyl)(phenylethynyl)sulfanes (2a'/2a = 1.6:1)

| Entry | Base   | Solvent (mL) | Yield of 3a (%)b |
|-------|--------|--------------|------------------|
| 1     | NaF    | THT (2 mL)   | 82               |
| 2     | NaO-t-Bu | THT (2 mL)   | 5                |
| 3     | Cs2CO3 | THT (2 mL)   | 0                |
| 4     |        | THT (2 mL)   | 88               |
| 5′    |        | DMF (2 mL)   | 6                |
| 6′    |        | Toluene (2 mL) | 3               |
| 7     |        | THT (4 mL)   | 94               |
| 8     |        | THT (6 mL)   | 94               |
| 9′    |        | THT (4 mL)   | 32               |
| 10′   |        | THT (4 mL)   | 92               |

*Reaction conditions: 1a (0.30 mmol), base (3.0 equiv), solvent (2 mL), 24 h, 120°C.
*Isolated yield.
*THT (5 equiv.).
*80 °C.
*140 °C.
Table 2. Ring-opening reaction of alkynyl bromides with THT

\[
\begin{align*}
\text{R} & \equiv \text{Br} + \text{S} & \rightarrow \text{R} & \equiv \text{S} \quad \text{Br} \\
\text{1} & & \text{120 °C} & \text{2}
\end{align*}
\]

| Compound | Yield (%) | Reaction Time (h) |
|----------|-----------|-------------------|
| 2a       | 92%       | 24 h              |
| 2c       | 81%       | 22 h              |
| 2e       | 90%       | 16 h              |
| 2g       | 85%       | 20 h              |
| 2i       | 91%       | 9 h               |
| 2k       | 92%       | 15 h              |
| 2m       | 63%       | 48 h              |
| 2o       | 73%       | 48 h              |
| 2b       | 76%       | 20 h              |
| 2d       | 95%       | 16 h              |
| 2f       | 86%       | 16 h              |
| 2h       | 86%       | 12 h              |
| 2j       | 85%       | 14 h              |
| 2l       | 88%       | 15 h              |
| 2n       | 73%       | 48 h              |
| 2p       | 74%       | 48 h              |

(Continued)
and (4-halobutyl)((4-methoxyphenyl)-ethynyl)sulfanes (2m'/2m = 1.6:1) were obtained in 70% and 55% yields, respectively. This result strongly suggests the involvement of an addition–elimination mechanism.

On the basis of the present results and the reported mechanism,\textsuperscript{[13]} we proposed an addition–elimination-induced nucleophilic substitution pathway to account for the product formation (Scheme 2). First, the reaction of phenylethynyl bromide with THT afforded the intermediate of 3 by nucleophilic addition reaction. Then, an elimination reaction took place and afforded the intermediate of

\begin{table}
\centering
\begin{tabular}{|c|c|}
\hline
Reaction conditions: 1a (0.3 mmol), THT (4 ml), 120 °C. & Isolated yield. \\
\hline
\end{tabular}
\end{table}
1-(phenylethynyl)tetrahydro-1H-thiophenium ion. Finally, the intermediate of sulfonium was attacked by a bromonium anion, and gave the ring-opening product.

CONCLUSIONS

In summary, the first additive-free method for synthesis of bromo-substituted alkynyl sulfides was developed. In the absence of any additives, alkynyl bromides served as a source of halogen and alkynyl in this process, and successfully underwent the ring opening reaction with THT to afford the corresponding bromo-substituted alkynyl sulfides in good to perfect yields. Work to probe the detailed mechanism and apply the reaction in organic synthesis is currently under way.

EXPERIMENTAL

$^1$H and $^{13}$C NMR spectra were recorded on a Bruker ARX500 spectrometer (FT, 500 MHz for $^1$H; 125 MHz for $^{13}$C) at room temperature, respectively. The $^1$HNMR spectra were taken in CDCl$_3$ and the chemical shifts are given in parts per million (ppm) with respect to tetramethylsilane (TMS) as an internal standard. The $^{13}$C NMR spectra were taken in CDCl$_3$ and the central peak of the solvent was adjusted to 77.00 ppm and used as a reference. Abbreviations for signal coupling are as follows: s, singlet; d, doublet; t, triplet; m, multiplet. High-resolution mass spectra (HRMS) were recorded on a Bruker Apex IV FTMS mass spectrometer using electrospray ionization (ESI). Melting points were measured uncorrected. Reactions were monitored by thin-layer chromatography (TLC) or GC-MS analysis. Column chromatography (petroleum ether/ethyl acetate) was performed on silica gel (200–300 mesh). Unless otherwise noted, commercially available starting materials were purchased from commercial sources and used without further purification. Compound 1 was prepared from terminal alkyne and NBS.$^{[14]}$

Typical Procedure for the Preparation of 2a

Phenylethynyl bromide (0.3 mmol) and THT (4 mL) were added to a Schlenk tube. Then the mixture was stirred at 120°C for the appropriate time. After the reaction was completed, the mixture evaporated under vacuum. The residue was purified by column chromatography on silica gel to provide the desired product (74.2 mg, 92%) as a yellow oil. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 7.42–7.40 (m, 2H), 7.29–7.28 (m, 3H), 3.45 (t, $J = 6.3$ Hz, 2H), 2.82 (t, $J = 6.8$ Hz, 2H), 2.08–2.02 (m, 2H), 2.00–1.95 (m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$: 131.38, 128.25, 128.04, 123.32, 93.30, 78.86, 34.70, 32.87, 30.94, 27.68; HRMS (ESI, $m/z$) calcd. for [C$_{12}$H$_{13}$BrS]$^+$: 268.9994; found 269.0000.

FUNDING

We thank the Natural Science Foundation of China (21072054), Ministry of Education of China (20094306120003, 213027A), Training Program Foundation for the Young Talents by Hunan Normal University of China (ET21003), Hunan Provincial Natural Science Foundation of China (12JJ2009), and Scientific Research
Fund of Hunan Provincial Education Department (12A095). Y. Yang also acknowledges Postgraduate Innovation Program of Hunan Province (CX2013B232) and Aid Program for Science and Technology Innovative Research Team in Higher Educational Institutions of Hunan Province for financial support.

**SUPPORTING INFORMATION**

Full experimental details and $^1$H and $^{13}$C NMR spectra can be accessed on the publisher’s website.

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