Catalyst- and Metal-Free Rapid Functionalizations of Alkynes Using $TsNBr_2$

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Received: 02.05.2013; Accepted after revision: 20.05.2013

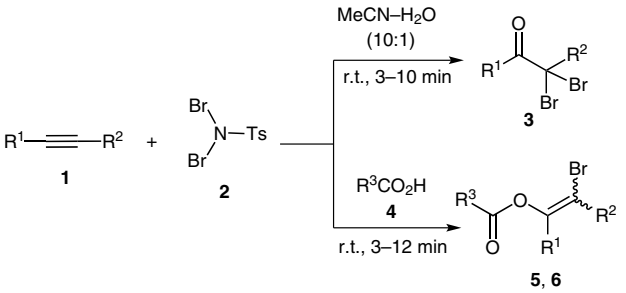
Abstract: A very rapid (3–12 min) and efficient method has been developed for a one-pot synthesis of α,α-dibromoalkanones and β-bromoenol alkanoates directly from alkynes using *N*,*N*-dibromo-*p*-toluenesulfonamide ($TsNBr_2$). The protocol is embellished with features like ambient temperature, high regioselectivity, operational simplicity, and metal- and catalyst-free conditions.

Key words: alkynes, $TsNBr_2$, α,α-dibromoalkanones, β-bromoenol alkanoates, catalyst-free conditions

Functionalization of alkynes to provide highly efficient access to complex frameworks has grasped the attention of the synthetic community tremendously over the recent years. Among these functionalizations, the transition-metal-catalyzed difunctionalization reactions of terminal alkynes have progressed rapidly during the last decade.[1] But these metal-based processes are generally not much preferred from a practical point of view, especially in the pharmaceutical industry where the removal of undesired metal contamination can be expensive.[2] Moreover, certain functional groups are incompatible with transition metals due to competing cross-coupling processes. On the other hand, the reactions involving the activation of alkynes using electrophilic halogen sources have emerged as powerful tools to achieve diverse functionalizations.[3] Use of stoichiometric amounts of simple electrophilic reagents such as electrophilic halogen sources can serve as excellent alternatives to the expensive transition-metal-catalyzed transformations keeping in line with environmental and economic issues.

α,α-Dibromoalkanones and β-haloenol alkanoates are important synthons in organic synthesis and pharmaceutical industry, the former being used for the synthesis of a variety of biologically active heterocyclic compounds.[4] The vinyl moiety in the latter makes β-haloenol acetate molecular skeletons versatile intermediates in organic synthesis[5,6] as they can be employed for transition-metal-catalyzed cross-coupling and halogen–metal exchange reactions.[7] Haloenol acetates are also known to be effective precursors of α-keto dianions.[6] Earlier, the syntheses of α,α-dibromoalkanones have been accomplished using reagents like benzyltrimethylammonium tribromide,[8] dioxane dibromide,[9] Selectfluor/KBr,[10] $PhI(OAc)_2$/NaX/CTAB[11] and oxone/NaBr.[12] These methods generally involve the use of expensive reagents, high temperatures, and microwave induction in some cases and suffer from long reaction times and limited substrate scope. Also, only a very few methods are available for the highly regio- and stereoselective synthesis of β-haloenol acetates.[13] Recent reports are from Jiang et al. for the synthesis of (*Z*)-β-haloenol acetates from terminal alkynes catalyzed by expensive silver salts[13b] and from Zhu and co-workers who have developed a convenient and practical method for the regio- and stereoselective synthesis of (*Z*)-β-haloenol acetates via the palladium-catalyzed coupling of alkynyl halides with allyl acetate under mild conditions.[13c] Thus, there is still scope for developing a metal-free efficient synthesis of α,α-dibromoalkanones and β-haloenol alkanoate molecular skeletons.

N,*N*-Dibromo-*p*-toluenesulfonamide ($TsNBr_2$) was first utilized as a reagent by Kharasch for the synthesis of 1-phenyl-2-(*p*-toluenesulfonamido)-1-bromoethane in 1939.[14] Also, there are reports on the preparation of haloamines and aziridines using *N*,*N*-dihalosulfonamides.[15] Recently, Phukan and co-workers have explicitly exploited the high reactivity of $TsNBr_2$ to carry out various organic transformations establishing its versatility and efficiency.[16] However, to the best of our knowledge there are no examples in the literature reporting the reaction of $TsNBr_2$ with simple alkynes; but highly functionalized alkynes have been reported to react with $TsNBr_2$ furnishing densely functionalized aziridine derivatives.[17] Prompted by the above points and in continuation of our work on one-pot synthetic methodologies,[18] we herein report the first very rapid, catalyst- and metal-free efficient synthesis of α,α-dibromoalkanones and β-bromoenol alkanoates from alkynes using $TsNBr_2$ as depicted in Scheme 1.



Scheme 1 Synthesis of α,α-dibromoalkanones and β-haloenol alkanoates

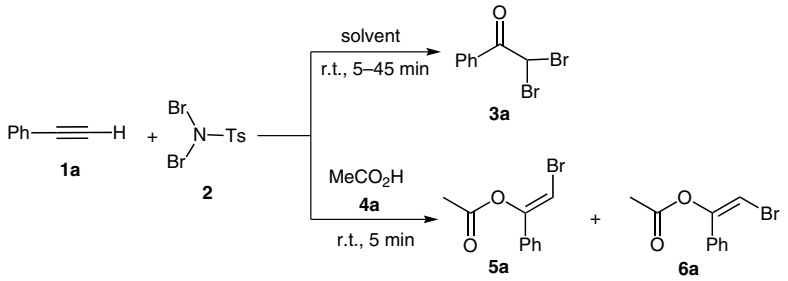
We began our study using one equivalent of phenylacetylene (**1a**) as a model substrate and one equivalent of $TsNBr_2$ (**2**) as a reagent in acetonitrile with few drops of

SYNLETT 2013, 24, 1558–1562
Advanced online publication: 20.06.2013
DOI: 10.1055/s-0033-1339194; Art ID: ST-2013-D0409-L

water at room temperature. A brisk reaction took place with the conversion of phenylacetylene (**1a**) into α,α-dibromoacetophenone (**3a**) as monitored by TLC. The reaction proceeded with almost complete consumption of $TsNBr_2$ but phenylacetylene still persisted in the reaction mixture. As a result, the substrate/reagent ratio was varied. When two equivalents of $TsNBr_2$ were used with one equivalent of phenylacetylene, the yield of the reaction increased from 45% to 87%. Encouraged by these results, we next decided to try the reaction in different solvents. The results of the study are compiled in Table 1. For obtaining α,α-dibromoalkanones, MeCN–H_2O (10:1) was identified as the best solvent system (Table 1, entry 2). Though a number of nucleophilic and non-nucleophilic solvents were tried, different and interesting results were obtained in glacial acetic acid (Table 1, entry 7). In this case, another product along with α,α-dibromoacetophenone (**3a**) was formed instantaneously which on ^1H NMR analysis was found to be a diastereomeric mixture of *E*- and *Z*-isomers of β-bromoenol acetates **5a** and **6a**, and could not be readily separated by column chromatography. The ^1H NMR spectrum of the purified mixture showed two singlets for the vinylic H (at δ = 6.55 and 6.31 ppm) and two singlets for the methyl protons (at δ = 2.34 and 2.17 ppm). For each pair, the downfield signal predominated (in a ratio of 2.5:1). In the NMR spectrum, NOE enhancement was observed for the aromatic protons upon irradiation of the major vinyl singlet at δ = 6.55, establishing the *Z*-configuration for the major isomer. The mixture could be separated by preparative chromatography.

The results appeared interesting due to two reasons: (i) β-bromoenol acetates **5a** and **6a** could be formed so easily and rapidly under metal-free conditions, and (ii) different results compared to the previous methods using other electrophilic halogen sources with alkynes were obtained. Previously, when oxidative bromination of phenylacetylene was carried out using Selectfluor/KBr, α,α-dibromoacetophenone (**3a**) was formed under neutral conditions in 30 minutes, whereas in the presence of acetic acid, a mixture of *cis*- and *trans*-1,2-dibromostyrene instead of β-bromoenol alkanoates was formed.[10] After establishing these results, the reaction was further optimized and examined for the substrate scope for obtaining α,α-dibromoalkanones and β-haloenol acetates separately. In the case of α,α-dibromoalkanones, the reaction worked well for terminal as well as nonterminal alkynes (Table 2).

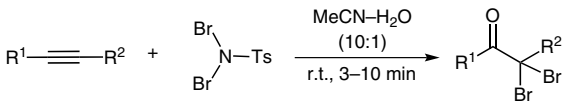
Table 1 Optimization of Solvents[20]



Entry	Solvent[a]	Time (min)	Yield (%)[b]
1	MeCN	5	45[c]
2	MeCN	5	87
3	EtOAc	8	82
4	dioxane	7	80
5	CH_2Cl_2	5	83
6	DMF	5	85
7	glacial AcOH[d]	5	10[e]
8	DMSO	15	34
9	EtOH	45	62
10	MeOH	30	64
11	MeCN[d]	15	12

[a] Conditions: 0.2 mL of H_2O were added to 2 mL of solvent.
[b] Isolated yield of purified product **3a**.
[c] Reaction conditions: phenylacetylene (**1a**, 1.0 mmol) and $TsNBr_2$ (**2**, 1.0 mmol) in 2 mL solvent with 0.2 mL H_2O.
[d] No H_2O was added.
[e] A mixture of products **5a** and **6a** was formed in 62% yield.

Table 2 Synthesis of α,α-Dibromoalkanones[20]

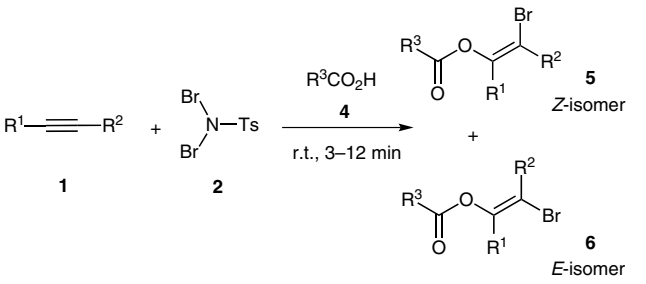


Entry	R^1	R^2	Product	Time (min)	Yield (%)[a,b]
1	Ph	H	**3a**	5	87
2	4-MeC_6H_4	H	**3b**	4	82
3	3-MeC_6H_4	H	**3c**	5	76
4	4-$MeOC_6H_4$	H	**3d**	4	72
5	4-$O_2NC_6H_4$	H	**3e**	3	74
6	Ph	Ph	**3f**	6	85
7	Ph	4-ClC_6H_4	**3g**	5	61
8	Pr	Pr	**3h**	7	78
9	Bu	H	**3i**	8	70
10	*t*-Bu	H	**3j**	10	68

[a] Isolated yield of purified product **3**.
[b] All compounds gave C, H, and N analyses within ±0.36%, and satisfactory spectral (IR, ^{1}H NMR, ^{13}C NMR, and EIMS) data.

In view of the prime significance of haloenol acetates as intermediates in organic synthesis and pharmaceutical industry, we first optimized the reaction conditions for their synthesis and also explored the substrate scope of the reaction. In order to obtain a better yield of β-bromoenol acetates, the substrate/reagent ratio was varied. When 1.0 equivalent of phenylacetylene was treated with 0.5 equivalents of $TsNBr_2$, the yield of β-bromoenol acetate increased from 62% to 85%. With the optimized reaction conditions in hand, we extended our synthetic protocol to a number of alkynes and carboxylic acids. The reaction worked well with different alkynes using glacial acetic acid, and the results are presented in Table 3 (entries1–7). In the case of aryl-substituted terminal alkynes, the *Z*-isomers **5** were obtained as the major product (Table 3, entries 1–5) which indicates that the electrophilic addition of Br^+ ion (generated from $TsNBr_2$) to alkynes formed the classical vinyl bromonium cation intermediate **7** susceptible to both *syn* and *anti* addition (Scheme 2). Also, the reaction displayed high regioselectivity which can be explained by considering the fact that the vinyl carbocation was stabilized by the aromatic ring. However, in the case of alkyl-substituted terminal alkynes, the bromoenol acetates were formed predominantly with *E*-configuration (Table 3, entries 6 and 7) suggesting that the reaction took place via a cyclic bromonium ion intermediate **8** (Scheme 2). The proposed mechanism is in accordance with earlier observations.[19] The reaction also proceeded if other carboxylic acids were used. When we used the optimized conditions for the reaction of phenylacetylene, $TsNBr_2$ and different acids as the solvent (2 mL), the corresponding β-bromoenol alkanoates were obtained in good yields (Table 3, entries 8–11).

Table 3 Synthesis of β-Bromoenol Alkanoates[21]



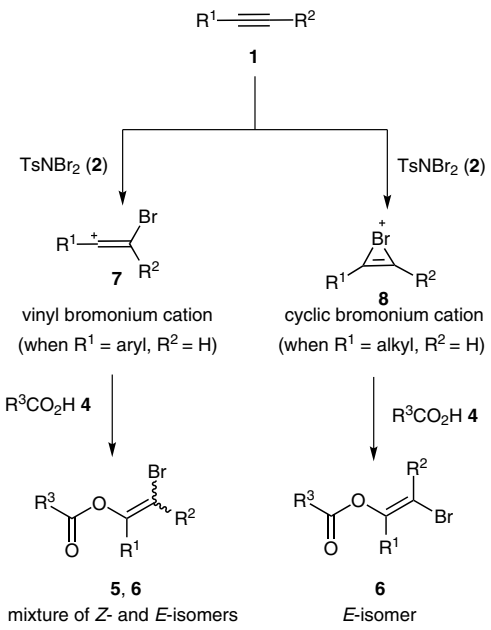
Entry	R^1	R^2	R^3	Product	Time (min)	Yield (%)[a,b]	Ratio[c] of **5a**/**6a**
1	Ph	H	Me	**5a**, **6a**	5	85	2.5:1
2	4-MeC_6H_4	H	Me	**5b**, **6b**	3	81	2.2:1
3	3-MeC_6H_4	H	Me	**5c**, **6c**	3	78	2.4:1
4	4-$MeOC_6H_4$	H	Me	**5d**, **6d**	5	75	2.6:1
5	4-$O_2NC_6H_4$	H	Me	**5e**, **6e**	4	76	2.7:1
6	Bu	H	Me	**5f**, **6f**	7	74	1:5.0
7	*t*-Bu	H	Me	**5g**, **6g**	8	71	1:4.8
8	Ph	H	H	**5h**, **6h**	5	63	2.2:1
9	Ph	H	Et	**5i**, **6i**	8	82	2.3:1
10	Ph	H	Pr	**5j**, **6j**	10	70	2.2:1
11	Ph	H	Bu	**5k**,**6k**	12	68	2.1:1

[a] Isolated yield of purified products **5** and **6**.
[b] All compounds are gave C, H, and N analyses within ±0.36%, and satisfactory spectral (IR, ^{1}H NMR, ^{13}C NMR and EIMS) data.
[c] As determined by ^{1}H NMR integration of the two stereoisomers **5** and **6** in the crude product.

In summary, a metal-free method for the synthesis of α,α-dibromoalkanones and β-bromoenol alkanoates from readily available alkynes using $TsNBr_2$ has been developed. The procedure is rapid, catalyst-free, and easy to perform at room temperature, and in the case of bromoenol alkanoates, it gives high regioselectivity and modest stereoselectivity. Further work to exploit this synthetic protocol using other nucleophiles is under way in our laboratory.

Acknowledgment

We sincerely thank SAIF, Punjab University, Chandigarh, for providing microanalyses and spectra. R. Chawla is grateful to the Department of the Science and Technology, New Delhi, for the award of Senior Research Fellowship (Reference No. SR/S1/OC-22/2010).



Scheme 2 Plausible mechanism for the formation of β-bromoenol alkanoates

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(20) **General Procedure for the Synthesis of α,α-Dibromoalkanones 3**

A mixture of alkyne **1** (1.0 mmol) and $TsNBr_2$ (**2**, 2.0 mmol) in MeCN (2 mL) with H_2O (0.2 mL) was stirred at r.t. for 3–10 min (Table 2). After completion of the reaction (monitored by TLC), H_2O was added and the mixture was extracted with EtOAc (3 × 5 mL). The combined organic phases were dried over anhyd Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude product was purified by silica gel column chromatography using a mixture of EtOAc–*n*-hexane (1:99) as eluent to afford an analytically pure sample of α,α-dibromoalkanones **3** (Table 2).

Characterization Data of Representative Compounds

Compound **3a**: viscous liquid; yield 87%. IR (neat):

ν_{max} = 3448, 2926, 1600, 1475, 1092 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.71 (s, 1 H), 7.49–7.57 (m, 2 H), 7.63–7.67 (m, 1 H), 8.08–8.10 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 39.7, 128.9, 129.8, 130.3, 134.7, 185.7. MS (EI): *m/z* = 276 [M^+], 278 [M^+ + 2]. Anal. Calcd for $C_8H_6Br_2O$: C, 34.57; H, 2.18. Found: C, 34.33; H, 2.26.

Compound **3h**: viscous liquid; yield 78%. IR (neat): ν_{max} = 2960, 2938, 2871, 1720, 1461, 1380, 1243, 1147, 1105, 627 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.99 (m, 6 H), 1.70 (m, 4 H), 2.43 (m, 2 H), 3.09 (t, *J* = 7.2 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.1, 13.6, 18.6, 20.7, 38.3, 46.8, 71.5, 198.0. MS (EI): *m/z* = 284 [M^+], 286 [M^+ + 2]. Anal. Calcd for $C_8H_{14}Br_2O$: C, 33.60; H, 4.93. Found: C, 33.52; H, 5.02.

(21) **General Procedure for the Synthesis of Bromoenol Alkanoates 5 and 6**

A mixture of alkyne **1** (2.0 mmol) and $TsNBr_2$ (**2**, 1.0 mmol) in carboxylic acid **4** (2 mL) was stirred at r.t. for 3–12 min (Table 3). After completion of the reaction (monitored by TLC), H_2O was added, and the mixture was extracted with EtOAc (3 × 5 mL). The combined organic phases were dried over anhyd Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude product was purified by preparative chromatography using a mixture of EtOAc–*n*-hexane (1:99) as eluent to afford an analytically pure sample of bromoenol alkanoates **5** and **6** (Table 3).

Characterization Data of Representative Compounds

Compound **5a**: yellow oil; yield 60%. IR (KBr): ν_{max} = 3095, 2928, 2852, 1765, 1625, 1436, 1370, 1180, 1036, 740, 694, 627, 569, 488 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.34 (s, 3 H), 6.55 (s, 1 H), 7.33–7.35 (m, 3 H), 7.37–7.41 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.5, 96.6, 124.3, 126.1, 128.5, 133.0, 150.2, 166.6. MS (EI): *m/z* = 240 [M^+], 242 [M^+ + 2]. Anal. Calcd for $C_{10}H_9BrO_2$: C, 49.82; H, 3.76. Found: C, 49.46; H, 3.82.

Compound **6a**: yellow oil; yield 24%. IR (KBr): ν_{max} = 3096, 2929, 2855, 1762, 1624, 1438, 1370, 1185, 1036, 740, 690, 625, 567, 489 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.17 (s, 3 H), 6.31 (s, 1 H), 7.34–7.43 (m, 4 H), 7.61–7.64 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.3, 94.6, 124.8, 128.5, 129.3, 133.2, 148.7, 167.3. MS (EI): *m/z* = 240 [M^+], 242 [M^+ + 2]. Anal. Calcd for $C_{10}H_9BrO_2$: C, 49.82; H, 3.76. Found: C, 49.55; H, 3.78.

Compound **5d**: yellow oil; yield 54%. IR (KBr): ν_{max} = 3094, 2938, 1765, 1609, 1510, 1458, 1370, 1035, 896, 835, 770, 658, 597, 512 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.31 (s, 3 H), 3.76 (s, 3 H), 6.37 (s, 1 H), 6.85 (d, *J* = 8.8 Hz, 2 H), 7.33 (d, *J* = 8.8 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.8, 55.2, 96.4, 113.5, 125.3, 126.3, 150.2, 160.1, 167.3. MS (EI): *m/z* = 270 [M^+], 272 [M^+ + 2]. Anal. Calcd for $C_{11}H_{11}BrO_3$: C, 48.73; H, 4.09. Found: C, 48.44; H, 4.12.

Compound **6d**: yellow oil; yield 20%. IR (KBr): ν_{max} = 3092, 2940, 1763, 1606, 1514, 1457, 1370, 1035, 898, 835, 770, 657, 595, 511 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.13 (s, 3 H), 3.80 (s, 3 H), 6.22 (s, 1 H), 6.87 (d, *J* = 9.2 Hz, 2 H), 7.56 (d, *J* = 8.0 Hz, 2 H).^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.5, 55.3, 94.4, 114.1, 125.8, 129.7, 148.5, 160.4, 168.6. MS (EI): *m/z* = 270 [M^+], 272 [M^+ + 2]. Anal. Calcd for $C_{11}H_{11}BrO_3$: C, 48.73; H, 4.09. Found: C, 48.40; H, 4.19.

