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Graphical Abstract

TsNBr$_2$ promoted decarboxylative bromination of α,β-unsaturated carboxylic acids

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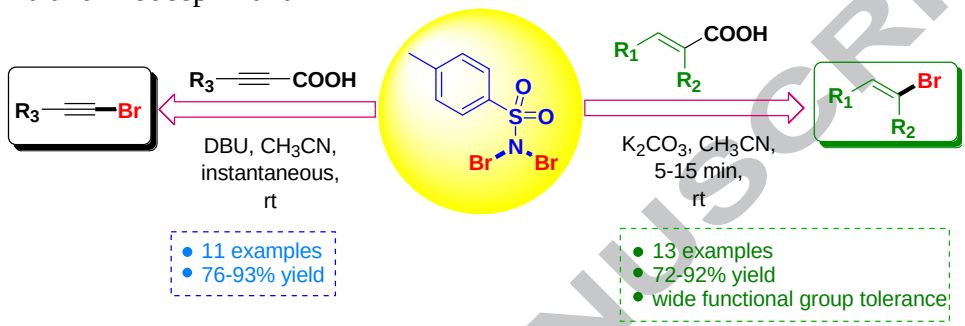

- 11 examples
- 76-93% yield

- 13 examples
- 72-92% yield
- wide functional group tolerance

$TsNBr_2$ promoted decarboxylative bromination of α,β-unsaturated carboxylic acids

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Abstract: A rapid process for decarboxylative bromination of α,β-unsaturated carboxylic acids have been developed using *N*,*N*-dibromo-*p*-toluenesulfonamide ($TsNBr_2$). Treatment of cinnamic acids with $TsNBr_2$ in presence of potassium carbonate in acetonitrile produces corresponding β-bromostyrenes at room temperature. Exclusive formation of (*E*)-β-bromostyrenes was observed in a stereoselective manner within a very short period of time (5-15 min). This method was further extended for obtaining 1-bromoalkynes from corresponding propiolic acids. Instantaneous formation of bromoalkynes was observed when the reaction was carried out in presence of DBU as a base in acetonitrile at room temperature. A wide variety of cinnamic acids and propiolic acids could be converted to corresponding β-bromostyrenes and 1-bromoalkynes respectively under mild reaction condition with high to excellent yield.

Key words: decarboxylative bromination, $TsNBr_2$, β-bromostyrene, 1-bromoalkyne, cinnamic acid, propiolic acid

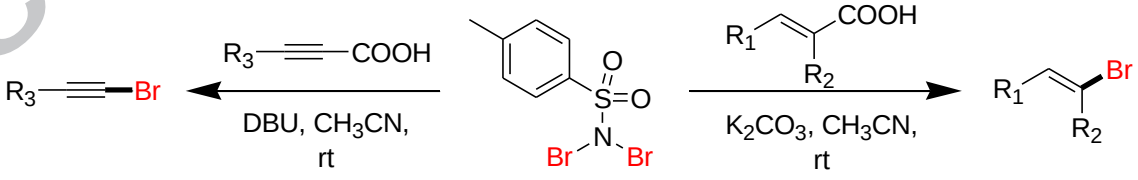
Halogenated organic substrates serve as an useful class of synthons for various organic transformations.[1] Synthesis of organic halides via decarboxylative bromination of α,β-unsaturated carboxylic acids, classically known as the Hunsdiecker reaction, is an important reaction for organic chemist.[2] The original Hunsdiecker reaction and subsequent developments for enhancing the synthetic utility of the classical reaction itself suffered from major drawbacks such as low yield of the desired product, high reaction temperature and use of toxic molecular bromine along with heavy metal salts.[3]

In past few decades, different methodologies involving radical or electrophilic halogenium ion pathway were developed to overcome the limitations associated with the classical processes.[4] Stoichiometric combination of a brominating agent and an additive viz. NBS/PhIO,[4c] TBAB/IBX,[4d] NBS/LiOAc,[4e,4f,4g,4h] NaBr/Oxone,[4i] TEAB/$PhI(OAc)_2$,[4j] KBr/Selectfluor,[4k] LiBr/CAN,[4l,4m] bis(collidine)bromine(I) hexafluorophosphate[4n], ethylenebis(N-methylimidazolium) ditribromide[4o] etc. were used for oxidative decarboxylative bromination of cinnamic acids. Roy and coworkers used NBS for bromodecarboxylation both under transition metal catalyzed and metal-free conditions.[5,6] Catalysts based on molybdenum and tungsten were also used for synthesis of β-bromostyrenes in presence of KBr and H_2O_2.[7,8] Synthetic methodologies assisted by ionic liquid [bmim][Br_3]/[bmim]Br, micellar media, ultrasonic reaction condition and electrolysis phenomena are also prevalent in the literature for synthesis of β-bromostyrenes from cinnamic acids.[9] But the major drawback associated with most of the protocol corresponds to the variation of reaction yield and time for different substrates depending upon the substitution pattern. In many cases, electron rich cinnamic acid produces good yield within a shorter period of time compared to cinnamic acid having electron withdrawing groups or halo functionalities. In certain cases the assistance of a micro-wave

condition is also necessary for specific substrates to minimize the reaction time for moderate yield of the desired product.

Telvekar and coworkers achieved considerable success in bromodecarboxylation of both electron rich and electron poor cinnamic acids using variety of reagent combinations.[10] They explored two different iodine reagents Dess-Martin-Perodinane (DMP) and diphosphorous tetraiodide (DPTI) respectively as oxidant for promoting the transformation using tetraethylammonium bromide (TEAB) as the bromine source,.[10a-b] DMP provided higher yield for electron rich cinnamic acids at a faster rate whereas DPTI gave good results for electron poor cinnamic acids and vice-versa. Further extending their bromodecarboxylative protocol, the same group also reported the transformation of cinnamic acids using $NaNO_2$ as catalyst in presence of 48% aq. HBr.[10c] However the efficiency of this protocol relies upon the use of O_2 as the external oxidant. So the development of a process which could minimize or overcome the inefficiency of the existing ones is of utmost importance.

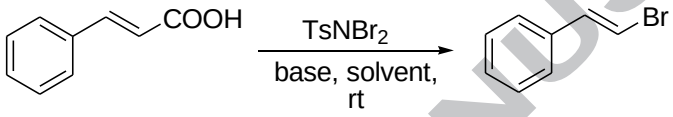
N,*N*-Dibromo-*p*-toluenesulfonamide ($TsNBr_2$), an efficient source of electrophilic bromine, has been established as a powerful and efficient reagent by our group for various organic transformations.[11,12] In continuation of our work on this reagent,[12] we are reporting herewith very fast and mild protocols for bromodecarboxylation reactions using $TsNBr_2$ as bromine source (Scheme 1).



Scheme 1. Decarboxylative bromination using $TsNBr_2$.

For the synthesis of β-bromostyrenes, initial investigations were carried out using cinnamic acid as the model substrate (Table 1). The experiment was carried out by adding $TsNBr_2$ (1 mmol) to a solution of cinnamic acid (1 mmol) and NaOH (2 mmol) in acetonitrile (2 mL) at room temperature. The reaction produced the desired product in 40% yield after 2h of reaction (Table 1, entry 1). When NaOH was replaced with equimolar amount of Et_3N, the reaction afforded 57% yield within 1h (Table 1, entry 2).

Table 1. Optimization of reaction condition for synthesis of β-bromostyrene from cinnamic acid.



S. No.	Base (equiv.)	$TsNBr_2$ (equiv.)	Solvent	Time (min)	% Yield[b]
1	NaOH (2)	1	CH_3CN	120	40
2	Et_3N (2)	1	CH_3CN	60	57
3	DBU (2)	1	CH_3CN	Instantaneous	94[c]
4	K_2CO_3 (2)	1	CH_3CN	5	85
5	K_2CO_3 (2)	1.05	CH_3CN	5	87
6	**K_2CO_3 (2)**	**1.1**	**CH_3CN**	**5**	**92**
7	K_2CO_3 (2)	1.2	CH_3CN	5	93
8	K_2CO_3 (1)	1.1	CH_3CN	15	77
9	K_2CO_3 (1.5)	1.1	CH_3CN	5	89
10	K_2CO_3 (2)	1.1	Ethylacetate	60	81
11	K_2CO_3 (2)	1.1	DCM	20	84

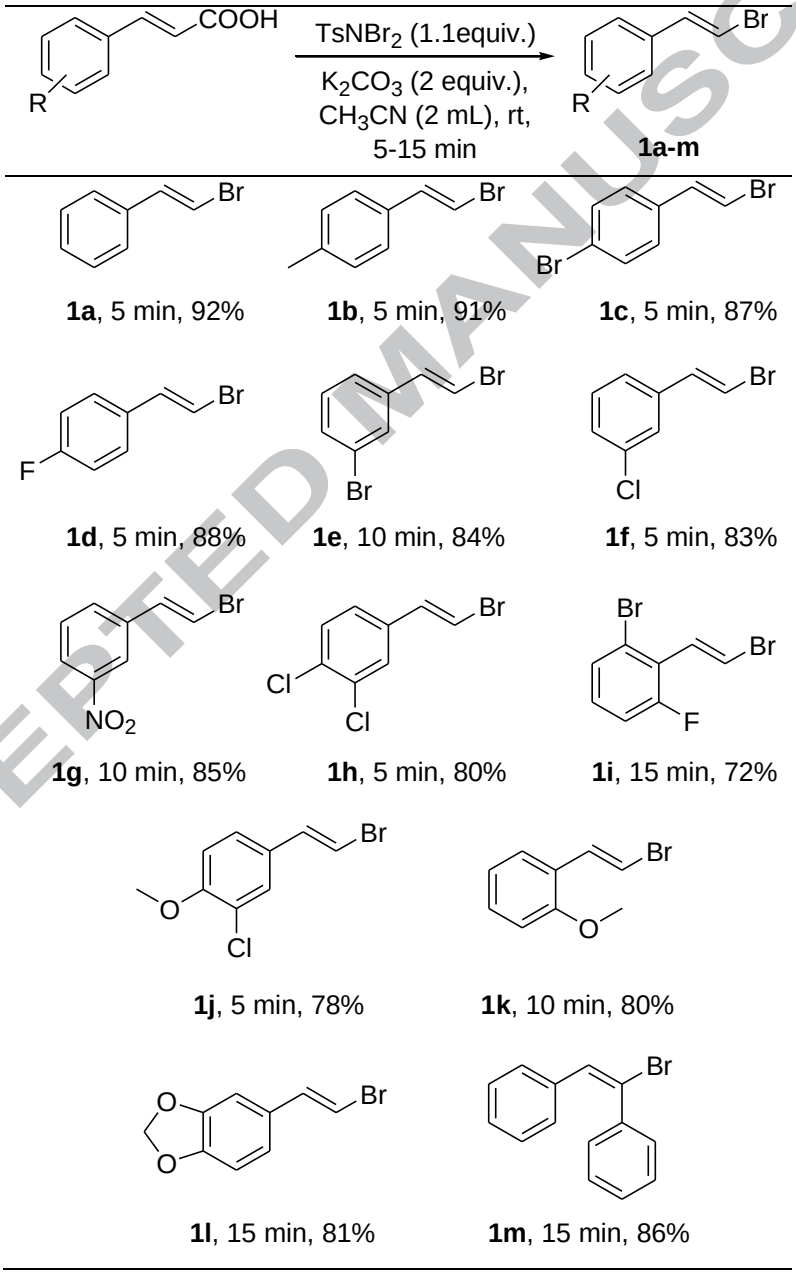
[a]Reaction condition: cinnamic acid (1mmol), solvent (2 mL), rt; [b]Isolated yield;
[c]mixture of cis:trans isomers (1:2).

Further modification of the reaction condition using DBU as base could produce corresponding β-bromostyrene instantaneously with a yield of 94% (Table 1, entry 3). However, the product was found to compose of a mixture of both the isomers E and Z in the ratio 2:1 respectively. Hence, the reaction was further examined in presence of 2 equivalent of K_2CO_3. This particular variation of the reaction condition led to exclusive formation of *trans* isomer of the desired β-bromostyrene (85%) within 5 min (Table 1, entry 4) at room temperature. In presence of DBU, the reaction is likely to proceed via formation of a carbocation intermediate[4s] where consecutive decarboxylation leads to the formation of a mixture of *cis-trans* isomers. Whereas, using K_2CO_3 as the base, a bromonium ion intermediate is expected where ring opening and decarboxylation occurs in a concerted manner. Next the reaction was investigated by varying the amount of $TsNBr_2$ and base to enhance the performance of the reaction (Table 1, entries 5-9). With 1.1 equivalent of $TsNBr_2$, the reaction provided 92% of β-bromostyrene (Table 1, entry 6). However with lower amount of K_2CO_3, diminishing yield of the desired product was observed (Table 1, entries 8-9). Effect of solvent in the reaction yield was also investigated using solvents like ethylacetate and DCM which produced inferior results with longer reaction time (Table 1, entries 10-11).

Having the optimized reaction condition in hand, the process was extended to a variety of cinnamic acids (Table 2).[13] From Table 2, it can be seen that the reaction completes within a very short time to produce corresponding β-bromostyrenes with excellent yield. The type and position of different functional groups in the aromatic ring do not have significant effect on the yield and reaction time. Cinnamic acids having both electron donating and electron withdrawing groups in the aromatic ring gave the desired product in excellent yield within a short time. Comparable reactivity was also observed for different halo-substituted cinnamic acids under the optimized reaction condition (Table 2, **1c-1f**). Moreover cinnamic acid having substitution in the double

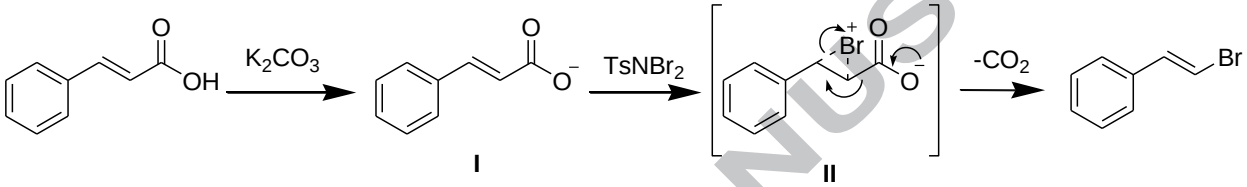
bond also gave the desired product in high yield (Table 2, **1m**). The method was found to be highly stereoselective producing exclusively the *trans*-isomer (E-isomer) of the desired product. Stereoselectivity was confirmed by analyzing the NMR spectral data and comparing with those reported in the literature.

Table 2. Substrate scope for synthesis of β-bromostyrene



[a]Reaction condition: cinnamic acid (1 mmol), $TsNBr_2$ (1.1 mmol), K_2CO_3 (2 mmol), CH_3CN (2 mL), rt.

A probable mechanistic pathway to explain the decarboxylative bromination mechanism is illustrated in Scheme 2. Initially, the base abstract the acidic proton to produce the carboxylate ion intermediate **I**, which upon subsequent reaction with $TsNBr_2$ results in the formation of bromonium intermediate **II**. Simultaneous ring opening of the bromonium ion along with elimination of carbon dioxide give the *trans*-β-bromostyrene.[4q]



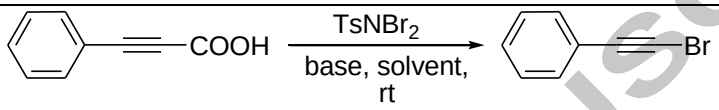
Scheme 2. Plausible mechanism for decarboxylative bromination of cinnamic acid.

Successful and quick transformation of various cinnamic acids to corresponding vinyl bromides encouraged us to extend the reaction to propiolic acids. So, we intended to examine the possibility of decarboxylative bromination of aryl propiolic acids using $TsNBr_2$. 1-Bromoalkynes serve as important building blocks in organic, material as well as polymer synthesis.[14] Compared to cinnamic acids, methods for decarboxylative bromination of propiolic acids are limited and only a few are reported in the literature.[4p,6b,7b,15] Lee *et al* established the same protocol using Oxone/NaBr for decarboxylative bromination of aryl propiolic acids after successful bromodecarboxylation of cinnamic acids.[16] Recently Liu's group reported copper mediated synthesis of 1-bromoalkynes from aryl propiolic acids in presence of pyridine under heating condition.[17]

While optimizing the reaction condition for cinnamic acid, we observed that using DBU as the base, the reaction goes for completion instantaneously to form a corresponding isomeric mixture of *cis*- and *trans*- vinyl bromide (Table 1, entry 3). However using propiolic acid as the

starting substrate, it invalidates the stereoselectivity factor. Hence, we examined the possibility of using DBU in case of propiolic acids. Initial reaction was carried out by treating a solution of phenyl propiolic acid (1 mmol) in acetonitrile (2 mL) with $TsNBr_2$ (1 mmol) in presence of DBU (1 mmol) at room temperature which produced corresponding 1-bromoalkyne instantaneously with 81% yield (Table 3, entry 1).

Table 3. Optimization of reaction condition for synthesis of 1-bromoalkyne from propiolic acid.



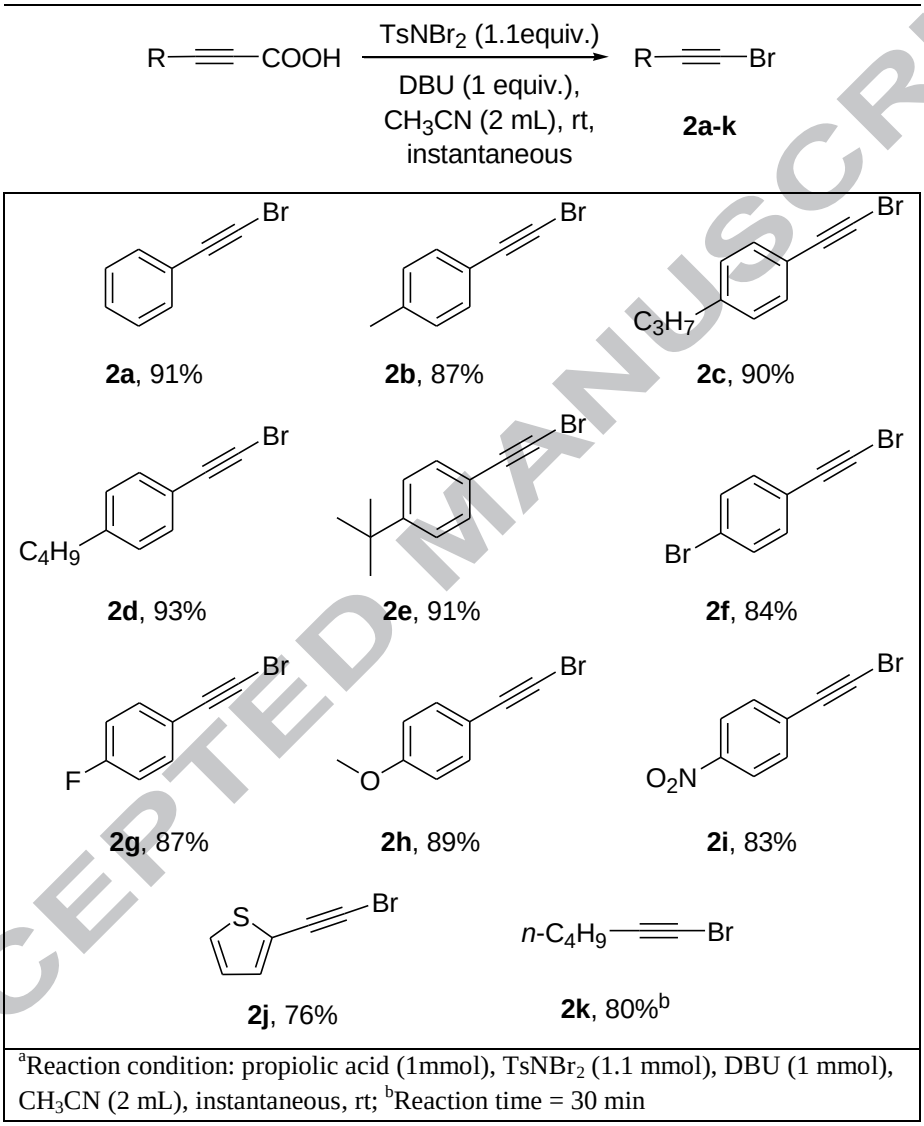
S. No.	Base (equiv.)	$TsNBr_2$ (equiv.)	Solvent	Time (min)	% yield[b]
1	DBU (1)	1	CH_3CN	Instantaneous	81
2	DBU (1)	1.05	CH_3CN	Instantaneous	87
3	**DBU (1)**	**1.1**	**CH_3CN**	**Instantaneous**	**91**
4	DBU (1)	1.2	CH_3CN	Instantaneous	91
5	DBU (1.2)	1.2	CH_3CN	Instantaneous	90
6	DBU (1)	1.2	DCM	10	81
7	DBU (1)	1.2	EtOAc	60	84
8	K_2CO_3 (1)	1.2	CH_3CN	30	87
9	Et_3N (1)	1.2	CH_3CN	60	64

[a]Reaction condition: phenyl propiolic acid (1 mmol); solvent (2 mL), rt; [b]Isolated yield

Enhancement in the reaction yield was observed by increasing the amount of $TsNBr_2$ to 1.1 mmol, with further increment being ineffective (Table 3, entries 2-4). The amount of base was also varied which could not afford any remarkable results (Table 3, entry 5). Solvents like DCM and ethylacetate were also effective but acetonitrile was found to be the better solvent with

respect to reaction time and yield (Table 3, entries 6-7). Investigation of other bases such as K_2CO_3 and Et_3N were also carried out which failed to produce any better results (Table 3, entries 8-9).

Table 4. Substrate scope for synthesis of 1-bromoalkyne



[a]Reaction condition: propiolic acid (1mmol), $TsNBr_2$ (1.1 mmol), DBU (1 mmol), CH_3CN (2 mL), instantaneous, rt; [b]Reaction time = 30 min

Under the optimized condition, the scope of the reaction was explored. A wide variety of phenyl propiolic acid having different functionalities could be transformed to corresponding 1-bromoalkyne in excellent yield (Table 4).[18] It was observed that the presence of electron

donating or withdrawing groups in the aromatic ring has no significant impact on the outcome of the reaction. Heterocyclic and alkyl propiolic acids were also tested, which participated well to produce the desired products in high yield (Table 4, **2j-k**). However, in case of alkyl propiolic acid, the reaction requires 30 min for completion.

In conclusion, simple and efficient protocols for decarboxylative bromination of α,β-unsaturated carboxylic acids have been established using $TsNBr_2$ in presence of K_2CO_3 at room temperataure. A comparable reactivity pattern was observed for different cinnamic acids irrespective of the substituent present in the aromatic ring. High stereoselectivity of the reaction with exclusive formation of *E*-isomer makes the process more useful. The procedure could further be extended for the synthesis of 1-bromoalkynes from aryl propiolic acids. The use of DBU as a base was found to be beneficial for transformation of propiolic acids to corresponding 1-bromoalkyne instantaneously with excellent yield. The significance of the process relies on very fast, mild and operationally simple reaction conditions along with wide substrates scope and excellent yield of the desired products.

Acknowledgement

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13. **General procedure for synthesis of β-Bromostyrene:** To a solution of cinnamic acid (1 mmol) in CH_3CN (2 mL), $TsNBr_2$ (1.1 mmol) and K_2CO_3 (2 mmol) was added and stirred at room temperature. After completion of the reaction (monitored by TLC), water was added. The aqueous layer was extracted using dichloromethane (30 mL), dried over anhydrous Na_2SO_4 and concentrated. The crude product was purified by flash chromatography using petroleum ether as eleunt.

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18. **General procedure for synthesis of 1-Bromoalkynes:** To a stirred solution of phenyl propiolic acid (1 mmol) in CH_3CN (2 mL), $TsNBr_2$ (1.1 mmol) and DBU (1 mmol) was added at room temperature. After completion of the reaction, the reaction mixture was diluted with ethyl

acetate and the organic layer was washed with water and dried over anhydrous Na_2SO_4. The concentrated crude product was purified by flash chromatography using petroleum ether as eleunt.

$TsNBr_2$ promoted decarboxylative bromination of α,β-unsaturated carboxylic acids

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Highlights

- Improved synthesis of (*E*)-β-bromostyrenes with wide substrate scope
- The reaction proceeds rapidly (5-15 min) with high stereoselectivity.
- Propiolic acids produces bromoalkynes instantaneously
- Mild reaction condition at room temperature
- The yields of the products are excellent.