


 Cite this: *RSC Adv.*, 2021, 11, 13292

 Received 11th December 2020
 Accepted 16th March 2021

DOI: 10.1039/d0ra10451e

rsc.li/rsc-advances

Cascade synthesis of 2,4-disulfonylpyrroles by the sulfonylation/[2 + 3]-cycloaddition reactions of *gem*-dibromoalkenes with arylsulfonyl methyl isocyanides†

 Parvin Salehi, Zahra Tanbakouchian, Noushin Farajinia-Lehi and Morteza Shiri *

An efficient cascade reaction involving sulfonylation and [2 + 3]-cycloaddition reactions of *gem*-dibromoalkenes with arylsulfonyl methyl isocyanides was described for the synthesis of 3-aryl-2,4-disulfonyl-1*H*-pyrroles. The main highlight of this study is the introduction of a new dual-functional reactivity of arylsulfonyl methyl isocyanides as the sulfonyl source as well as a 1,3-dipolar reagent in the same reaction. This system is facilitated by Cs₂CO₃ mediation in DMSO and 100 °C conditions.

Introduction

Since its first isolation from bone pyrolysis in 1857, the pyrrole unit was identified as a fundamental substructure of numerous important natural and bioactive unnatural products.¹ Lamellarin R as an anti-cancer and anti-HIV alkaloid,² and other active pyrrolizidine alkaloids, chlorophyll, cobalamin (vitamin B₁₂), heme and bile pigments are some of the well-known naturally occurring pyrrole derivatives.³ Hence, numerous syntheses for substituted pyrroles have been reported including classical Hantzsch,⁴ Knorr⁵ and Paal-Knorr⁶ methods and some alternative procedures such as aza-Wittig, coupling, condensation and annulation reactions.⁷ Owing to the practicality and commercial accessibility of their compounds, isocyanides and π systems have been demonstrated to be attractive functionalities for heterocyclic cycloaddition reactions that due to appropriate atom-economy are considered as an ideal approach for the direct synthesis of substituted pyrroles.⁸

In particular, recently, activated isocyanides, including α -acidic isocyanides with additional functionalities owing to their 1,3-dipolar nature and efficient cooperation in [3 + 2] cycloaddition reactions have attracted considerable attention of numerous synthetic researchers.⁹ Amongst these structures, arylsulfonyl methyl isocyanides (ASMIC), particularly *p*-toluenesulfonylmethyl isocyanide (TosMIC), are one of the most impressive reagents from both the stability and reactivity point of views.¹⁰ TosMIC, as an odorless derivative of isocyanides can afford a multitude of reactions *via* its three different functionalities of α -acidic carbon, isocyanide and sulfonyl groups.¹¹ Two

features of less sterically congested α -C–H bonds and enhanced electrophilicity as a consequence of additional sulfonyl functionality distinguish this reactive reagent from other alkyl isocyanides (Fig. 1).^{12,13}

Moreover, sulfonyl function as a leaving group can offer TosMIC an efficient source of sulfonyl group, whereby it can act as a dual reagent and/or as a sulfonylation reagent.¹² In this regard, Bi *et al.* introduced the dual role of TosMIC in a cascade reaction with propargylic alcohols, wherein TosMIC acted as a reagent for allenylative and sulfonylation in the presence of Ag₂CO₃ to give (*E*)-vinyl sulfones (Scheme 1, eqn (1)).¹⁴ Also, recently, our group investigated the behavior of TosMIC in treatment by 2-chloroquinoline-3-carbaldehydes, and the result was in tandem with the van Leusen/ring-closing procedure and tosylation to create 5-(2-tosylquinolin-3-yl)oxazoles, which testified to the dual-functional reactivity of mentioned isocyanide (Scheme 1, eqn (2)).¹⁵

As our ongoing effort to explore the novel synthetic application of 1,1-dibromoalkenes, we have previously investigated the reaction of this alkenes with two reagents of alkyl isocyanides and sodium sulfonates, which in the former, 3-(hetero) arylpropynamides furnished from a palladium-catalyzed cross-coupling reaction,¹⁶ and the latter involved a sulfonylation to yield the desired 1-bromo-1-sulfonylalkenes.¹⁷ *gem*-Dibromo-1-alkenes, which can be easily generated from the treatment of aldehydes or ketones with CBr₄/PPh₃,¹⁸ can act as an alternative

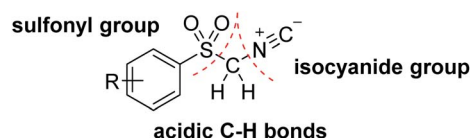
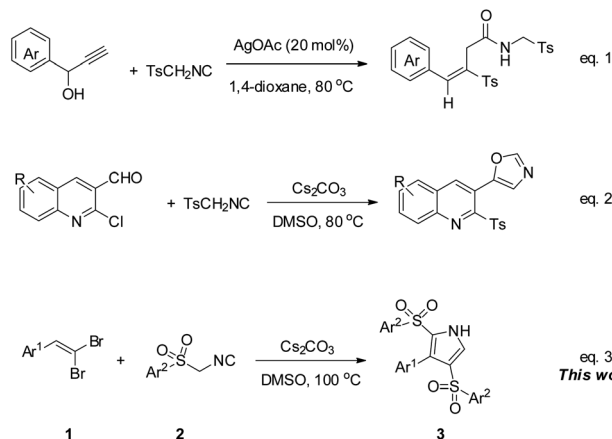


Fig. 1 Structure of TosMIC.

Department of Chemistry, Faculty of Physics and Chemistry, Alzahra University, Vanak, Tehran 1993893973, Iran. E-mail: mshiri@alzahra.ac.ir

† Electronic supplementary information (ESI) available. See DOI: 10.1039/d0ra10451e





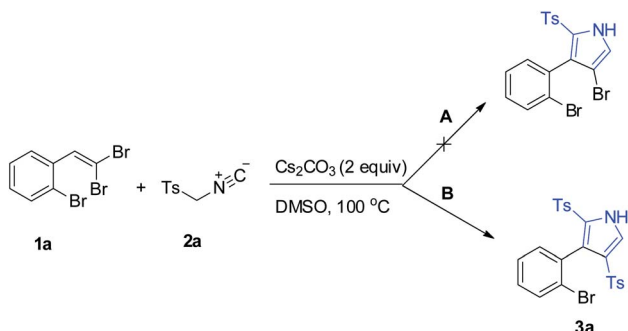
Scheme 1 ASMIC as a dual-functional reactive starting material in the same reaction.

resource of activated alkene and alkyne moieties.¹⁹ Encouraged by these findings, we envisaged that arylsulfonyl methyl isocyanides might react with 1,1-dibromoalkenes as a dual functional reagent, both as a [1,3]-dipolar and as a sulfonyl source in a cascade process. To our delight, 3-aryl-2,4-disulfonyl-1H-pyrroles were isolated up to 90% yield from the mentioned reaction under Cs₂CO₃ condition at 100 °C (Scheme 1, eqn (3)).

Results and discussion

Inspired by our previously developed conditions,¹⁷ we started our survey by the cycloaddition of 1-bromo-2-(2,2-dibromovinyl)benzene (**1a**)²⁰ and TosMIC (**2a**) under Cs₂CO₃ condition (2 equiv.) in DMSO at 100 °C. Two different routes were envisageable for the reaction (Scheme 2). What actually rationalizes the formation of **3a** product (route B) is the occurrence of an additional step of the tosylation procedure, which affirms the dual role of TosMIC. Noteworthy, in this transformation, no by-product outcome from the direct [2 + 3]-cycloaddition of acetylene bromide (route A) was observed.

Our initial study focused on the exploration of optimal reaction conditions. As summarized in Table 1, to first evaluate the base efficiency, the reaction was conducted in a base-free



Scheme 2 Formation of 2,4-ditosyl-1H-pyrrole instead of 4-bromo-2-tosyl-1H-pyrrole.

Table 1 Optimization of reaction condition^a

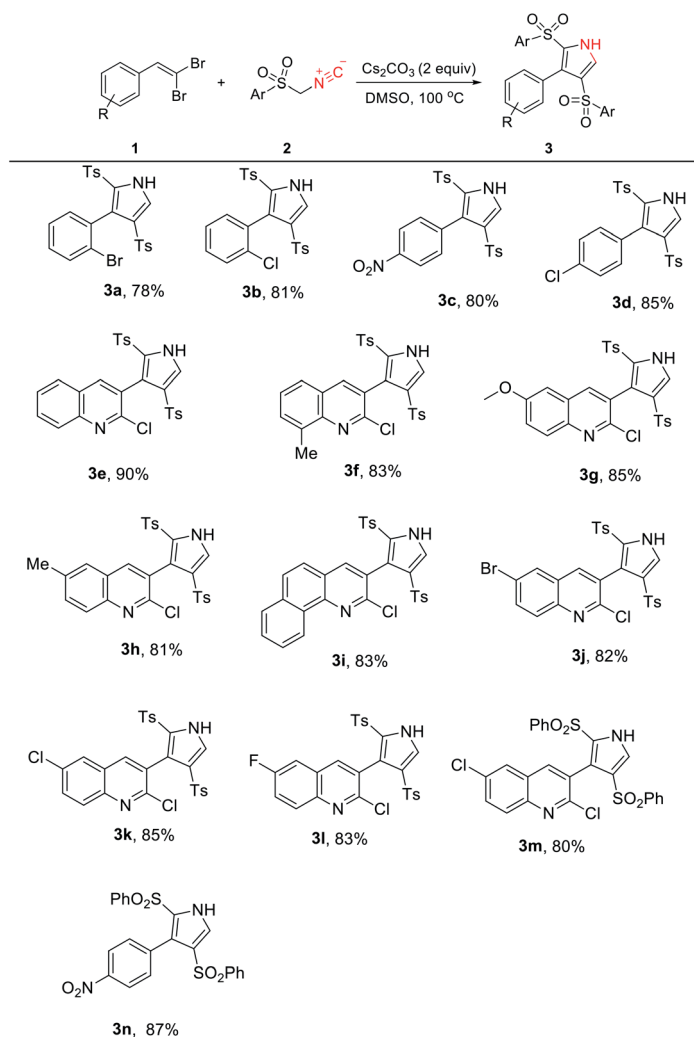
Entry	Base (equiv.)	Solvent	Temp. (°C)	Yield ^b (%)
1	—	DMSO	100	—
2	CsF (2)	DMSO	100	20
3	Cs ₂ CO ₃ (2)	DMSO	100	78
4	Et ₃ N (2)	DMSO	100	Trace
5	K ₂ CO ₃ (2)	DMSO	100	15
6	Na ₂ CO ₃ (2)	DMSO	100	12
7	NaOAc (2)	DMSO	100	40
8	^t BuONa (2)	DMSO	100	56
9	^t BuOK (2)	DMSO	100	65
10	Cs ₂ CO ₃ (1)	DMSO	100	50
11	Cs ₂ CO ₃ (2)	DMF	100	75
12	Cs ₂ CO ₃ (2)	Toluene	Reflux	Trace
13	Cs ₂ CO ₃ (2)	CH ₃ CN	Reflux	25
14	Cs ₂ CO ₃ (2)	DMSO	rt	—

^a Reaction conditions: **1a** (1.0 mmol), **2a** (2.0 mmol), base (2 equiv.), solvent (4.0 mL), temp. (100 °C) (bath temperature), 3–6 h. ^b Isolated yields.

media whereby no desired product was detected (Table 1, entry 1). This result encouraged us to screen numerous bases involving CsF, Cs₂CO₃, Et₃N, K₂CO₃, Na₂CO₃, NaOAc, ^tBuONa, and ^tBuOK at 100 °C (Table 1, entries 2–9) and the best yield of **3a** was obtained using Cs₂CO₃ in 78% yield (Table 1, entry 3). Notably, the counterion effect of the basic anions was compared, and the results showed its effective role in proceeding the reaction to high yields as the counterion size increased (Na, K to Cs). Also, when the amount of Cs₂CO₃ was decreased, the result reduced to 50% yield (Table 1, entry 10). Changing the reaction media to other solvents such as DMF, toluene or CH₃CN, was not very successful to improve the product yield (Table 1, entries 11–13). In fact, the reaction failed in toluene (Table 1, entry 12). Implementing the reaction in ambient temperature offered no conversion, proving the distinct critical role of temperatures for the reaction to proceed (Table 1, entry 14). Summarizing the observations, we found that 2 equivalents of Cs₂CO₃ in DMSO at 100 °C were the best conditions listed in entry 3 and were chosen for the following explorations.

Under the determined optimal conditions, we perused the scope of reaction by numerous available starting materials. As illustrated in Table 2, the process was readily extended to a range of substituted aromatic and heteroaromatic *gem*-dibromoalkenes (**1**) with TosMIC (**2a**). The steric effects derived from *ortho*-substitutions and quinoline rings attached to the alkene had nearly no influence on these transformations (**3a–3m**). Similar to TosMIC, phenylsulfonylmethyl isocyanide (**2b**) also participated in the cascade reaction with 2,6-dichloro-3-(2,2-dibromovinyl)quinoline and 1-(2,2-dibromovinyl)-4-



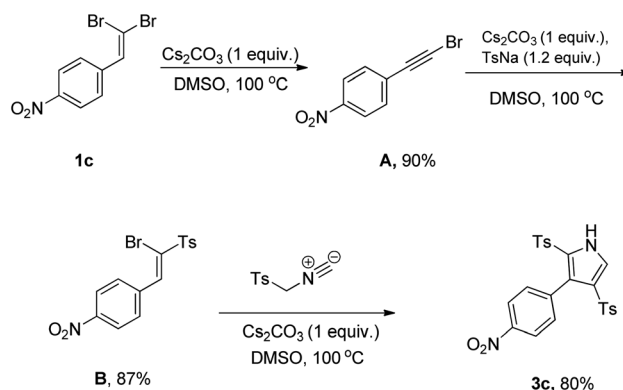
Table 2 Scope of the synthesis of numerous 3-aryl-2,4-disulfonyl-1H-pyrroles **3**^a

^a Reaction conditions: **1** (1.0 mmol), **2** (2.0 mmol), Cs_2CO_3 (2 equiv.), DMSO (4.0 mL), temp. (100 °C) (bath temperature), 3–6 h.

nitrobenzene without any difficulties, giving rise to the corresponding products in 80% and 87% yields, respectively (**3n** and **3o**). Notably, the presence of a Me or an OMe group on the aryl ring of the *gem*-dibromoalkene did not afford the expected results.

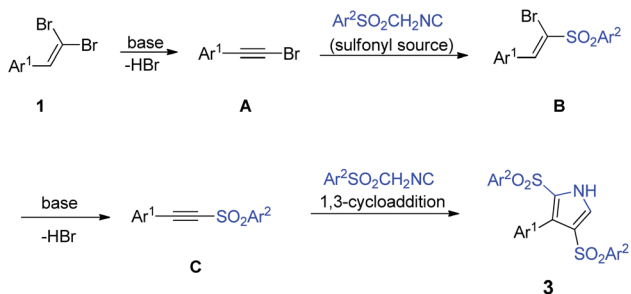
Further experiments were performed based on a designed series of control experiments to provide some insights into the reaction profile, as depicted in Scheme 3. Initially, the conversion of 1-(2,2-dibromovinyl)-4-nitrobenzene (**1c**) as the only starting material under the established condition was investigated, leading to the detection of desired acetylene bromide **A**. By assuming the following sulfonylation, we treated the resulting acetylene with sodium *p*-toluenesulfonate (**TsNa**) as the tosyl source based on our previously related study.¹⁷ Similarly, we found vinyl sulfone **B** as the only product, which in continuation, reacted with TosMIC in optimal conditions furnishing compound **3c** in 80% yield.

Regarding the above-described findings, we suggested a plausible mechanism for this cascade reaction initiated by the HBr elimination process of 1,1-dibromoalkene **1** in an alkali



Scheme 3 A designed sequences of control experiments for mechanistic investigation.





Scheme 4 A plausible reaction mechanism.

media to form acetylene bromide **A** (Scheme 4). Subsequently, in a domino manner, TosMIC **2a** acts as a sulfonyl source to render intermediate **B**, which undergoes the second HBr elimination to generate the sulfonyl acetylene **C** by Cs_2CO_3 assistance. Eventually, the [2 + 3]-cycloaddition of acetylene **C** with another TosMIC furnishes the desired product **3**.

Conclusions

We introduced a novel and straightforward strategy for the preparation of 3-aryl-2,4-disulfonyl-1H-pyrroles in high efficiency, which took advantage of a dual functional reactivity of arylsulfonyl methyl isocyanides against 1,1-dibromoalkenes under basic conditions. This process was facilitated in the presence of Cs_2CO_3 , and its extensibility was evaluated for numerous starting materials. Furthermore, based on preliminary investigations of the reaction profile, a possible mechanism was proposed involving acetylenic intermediates. This report can be helpful to boost the practical developments of arylsulfonyl methyl isocyanides chemistry.

Conflicts of interest

There are no conflict to declare.

Acknowledgements

Alzahra University and INSF (Iran National Science Foundation) are gratefully acknowledged for their support.

References

- (a) V. Estevez, M. Villacampa and J. C. Menendez, Multicomponent reactions for the synthesis of pyrroles, *Chem. Soc. Rev.*, 2010, **39**, 4402; (b) S. D. Joshi, U. A. More, V. H. Kulkarni and T. M. Aminabhavi, Pyrrole: chemical synthesis, microwave assisted synthesis, reactions and applications: a review, *Curr. Org. Chem.*, 2013, **17**, 2279; (c) J. T. Gupton, Pyrrole natural products with antitumor properties, in *Heterocyclic Antitumor Antibiotics*, Springer, 2006, pp. 53–92; (d) S. S. Gholap, Pyrrole: an emerging scaffold for construction of valuable therapeutic agents, *Eur. J. Med. Chem.*, 2016, **110**, 13; (e) V. Bhardwaj, D. Gumber, V. Abbot, S. Dhiman and P. Sharma, Pyrrole:

a resourceful small molecule in key medicinal hetero-aromatics, *RSC Adv.*, 2015, **5**, 15233; (f) S. Ahmad, O. Alam, M. J. Naim, M. Shaquiquzaman, M. M. Alam and M. Iqbal, Pyrrole: an insight into recent pharmacological advances with structure activity relationship, *Eur. J. Med. Chem.*, 2018, **157**, 527.

- M. Iwao, T. Fukuda and F. Ishibashi, Synthesis and biological activity of lamellarin alkaloids: an overview, *Heterocycles*, 2011, **83**, 491.
- (a) V. Estévez, M. Villacampa and J. C. Menéndez, Recent advances in the synthesis of pyrroles by multicomponent reactions, *Chem. Soc. Rev.*, 2014, **43**, 4633; (b) J. R. Liddell, Pyrrolizidine alkaloids, *Nat. Prod. Rep.*, 2001, **18**, 441; (c) B. Forte, B. Malgesini, C. Piutti, F. Quartieri, A. Scolaro and G. Papeo, The pyrrole-imidazole alkaloids, *Mar. Drugs*, 2009, **7**, 705; (d) P. W. Le Quesne, Y. Dong and T. A. Blythe, *Recent Research on Pyrrole Alkaloids*, Pergamon Press, Oxford, 1999, vol. 13; (e) V. F. Ferreira, M. C. B. V. de Souza, A. C. Cunha, L. O. R. Pereira and M. L. G. Ferreira, Recent advances in the synthesis of pyrroles, *Org. Prep. Proced. Int.*, 2001, **33**, 411.
- A. Hantzsch, *Ber. Dtsch. Chem. Ges.*, 1890, **23**, 1474.
- L. Knorr, Synthese von pyrrolderivaten, *Ber. Dtsch. Chem. Ges.*, 1884, **17**, 1635.
- C. Paal, Synthese von Thiophen-und Pyrrolderivaten, *Ber. Dtsch. Chem. Ges.*, 1885, **18**, 367.
- (a) A. R. Katritzky, J. Jiang and P. J. Steel, 1-Aza-1,3-bis(triphenylphosphoranylidene)propane: a novel: CHCH_2N : synthon, *J. Org. Chem.*, 1994, **59**, 4551; (b) E. Baltazzi and L. I. Krimen, Recent Advances in the Chemistry of Pyrrole, *Chem. Rev.*, 1963, **63**, 511; (c) B. A. Trofimov, I. M. Al'bina, E. Y. Schmidt and L. N. Sobenina, *Chemistry of Pyrroles*, CRC press, 2014; (d) F. J. Leeper and J. M. Kelly, Synthesis of 3,4-disubstituted pyrroles. A review, *Org. Prep. Proced. Int.*, 2013, **45**, 171.
- (a) A. V. Lygin and A. de Meijere, Isocyanides in the synthesis of nitrogen heterocycles, *Angew. Chem., Int. Ed.*, 2010, **49**, 9094; (b) S. Sadjadi, M. M. Heravi and N. Nazari, Isocyanide-based multicomponent reactions in the synthesis of heterocycles, *RSC Adv.*, 2016, **6**, 53203; (c) M. Shiri, N. Farajinia-Lehi, P. Salehi and Z. Tanbakouchian, Transition Metal and Inner Transition Metal Catalyzed Amide Derivatives Formation through Isocyanide Chemistry, *Synthesis*, 2020, **52**, 3162.
- (a) I. V. Efimov, L. N. Kulikova, D. I. Zhilyaev and L. G. Voskressensky, Recent Advances in the Chemistry of Isocyanides with Activated Methylene Group, *Eur. J. Org. Chem.*, 2020, 7284; (b) J.-Y. Liao, P.-L. Shao and Y. Zhao, Catalytic divergent synthesis of 3H or 1H pyrroles by [3 + 2] cyclization of allenates with activated isocyanides, *J. Am. Chem. Soc.*, 2015, **137**, 628; (c) M. Gao, C. He, H. Chen, R. Bai, B. Cheng and A. Lei, Synthesis of Pyrroles by Click Reaction: Silver-Catalyzed Cycloaddition of Terminal Alkynes with Isocyanides, *Angew. Chem., Int. Ed.*, 2013, **52**, 6958; (d) J. Cai, H. Bai, Y. Wang, X. Xu, H. Xie and J. Liu, Base-mediated regioselective [3 + 2] annulation of ketenimines and isocyanides: efficient synthesis of 1,4,5-



- trisubstituted imidazoles, *Chem. Commun.*, 2019, **55**, 3821; (e) X. Meng, P. Liao, J. Liu and X. Bi, Silver-catalyzed cyclization of 2-pyridyl alkynyl carbinols with isocyanides: divergent synthesis of indolizines and pyrroles, *Chem. Commun.*, 2014, **50**, 11837.
- 10 (a) A. D. Mathiyazhagan and G. Anilkumar, Recent advances and applications of p-toluenesulfonylmethyl isocyanide (TosMIC), *Org. Biomol. Chem.*, 2019, **17**, 6735; (b) D. V. Leusen and A. M. V. Leusen, Organic reactions 2001. Synthetic uses of tosylmethyl isocyanide (TosMIC), *Org. React.*, 2001, **57**, 417; (c) T. Kaur, P. Wadhwa and A. Sharma, Arylsulfonyl methyl isocyanides: a novel paradigm in organic synthesis, *RSC Adv.*, 2015, **5**, 52769.
- 11 D. V. Aderohunmu, T. T. Odotola, O. O. Ajani and E. F. Adebisi, TosMIC reagent: an excellent precursor in the synthesis of biologically active heterocycles, *Rasayan J. Chem.*, 2019, **12**, 1919.
- 12 K. Kumar, TosMIC: A Powerful Synthone for Cyclization and Sulfonylation, *ChemistrySelect*, 2020, **5**, 10298.
- 13 V. V. R. Reddy, p-Toluenesulfonylmethyl isocyanide (TosMIC), *Synlett*, 2005, 363.
- 14 H. Bounar, Z. Liu, L. Zhang, X. Guan, Z. Yang, P. Liao, X. Bi and X. Li, Silver-catalyzed cascade reaction of tosylmethyl isocyanide (TosMIC) with propargylic alcohols to (E)-vinyl sulfones: dual roles of TosMIC, *Org. Biomol. Chem.*, 2015, **13**, 8723.
- 15 Z. Yasaei, Z. Mohammadpour, M. Shiri, Z. Tanbakouchian and S. Fazlzadeh, Isocyanide reactions toward the synthesis of 3-(oxazol-5-yl)quinoline-2-carboxamides and 5-(2-tosylquinolin-3-yl)oxazole, *Front. Chem.*, 2019, **7**, 433.
- 16 P. Salehi and M. Shiri, Palladium-Catalyzed Regioselective Synthesis of 3-(Hetero)Arylpropynamides from gem-Dibromoalkenes and Isocyanides, *Adv. Synth. Catal.*, 2019, **361**, 118.
- 17 M. Shiri, P. Salehi, Z. Mohammadpour, P. Salehi and B. Notash, Cs₂CO₃-Mediated Regio- and Stereoselective Sulfonylation of 1,1-Dibromo-1-alkenes with Sodium Sulfonates, *Synthesis*, 2021, **53**, 1149.
- 18 E. J. Corey and P. L. Fuchs, Synthetic method for conversion of formyl groups into ethynyl groups, *Tetrahedron Lett.*, 1972, **36**, 3769.
- 19 (a) M. M. Heravi, S. Asadi, N. Nazari and B. Malekzadeh Lashkariani, Developments of Corey-Fuchs reaction in organic and total synthesis of natural products, *Curr. Org. Chem.*, 2015, **19**, 2196; (b) G. Chelucci, Synthesis and metal-catalyzed reactions of gem-dihalovinyl systems, *Chem. Rev.*, 2012, **112**, 1344.
- 20 (a) N. B. Desai, N. McKelvie and F. Ramirez, A new synthesis of 1,1-dibromoolefins via phosphine-dibromomethylenes. The reaction of triphenylphosphine with carbon tetrabromide, *J. Am. Chem. Soc.*, 1962, **84**, 1745; (b) D. Nandini, M. Asthana, K. Mishra, R. P. Singh and R. M. Singh, Temperature dependent selective synthesis of linear 2-bromo and 2-alkoxyfuro[2,3-b]quinolines: reaction of 3-(2,2-dibromovinyl)-quinoline-2(1H)-ones with alcoholic KOH, *Tetrahedron Lett.*, 2014, **55**, 6257.

