Organic & Biomolecular Chemistry

ROYAL SOCIETY OF CHEMISTRY

PAPER

View Article Online
View Journal | View Issue

Cite this: *Org. Biomol. Chem.*, 2021, **19**, 2688

Monofluorinated 5-membered rings *via* fluoromethylene transfer: synthesis of monofluorinated isoxazoline *N*-oxides†

Arturs Sperga, Armands Kazia and Janis Veliks *

Received 12th February 2021,
Accepted 26th February 2021

DOI: 10.1039/d1ob00270h

rsc.li/obc

The synthesis of five-membered rings using fluoromethylene transfer chemistry is an attractive method for building fluorinated products of high value. This work demonstrates for the first time that one-fluorine-one-carbon modification of a substrate could be a viable strategy to access monofluorinated five-membered rings. The synthetic methodology was developed to access monofluorinated isoxazoline-*N*-oxides in one step starting from substituted 2-nitroacrylates using fluoromethylsulfonium reagents.

Fluorine atoms are of increasing prevalence in drug molecules;[1] thus, the development of new strategies for obtaining fluorinated organic compounds is of critical importance in medicinal chemistry,[2] agrochemistry,[3] and materials.[4] Strategies for synthesizing fluorinated 5-membered rings[5] can be classified into two major categories (Fig. 1A): (1) synthetic routes that involve a direct fluorination step (formation of C–F bonds) and[6] (2) the utilization of fluorinated building blocks.[7] Both of these approaches are used to access high-value fluorine-containing products.[5c] Recently, we have developed reactions involving fluoromethylene transfer[8] (mimicking fluorocarbene chemistry) where the simplest C–F-containing building block (CHF:) is incorporated into a substrate— the one-fluorine-one-carbon modification of a target structure which could be considered as a middle ground of the aforementioned classical approaches. To date, fluoromethylene transfer has been successfully demonstrated only for the synthesis of vinyl fluorides[9] and monofluorinated 3-membered rings.[10] To the best of our knowledge, 5-membered ring formation by such a strategy has not been demonstrated thus far. The isoxazole scaffold[11] can be found among the list[12] of the most commonly used heterocycles in pharmaceuticals, and its partially saturated analog isoxazoline[13] derivatives also have relevant biological activity, as illustrated in Fig. 1B.[14] Despite the fact that perfluoro- and trifluoromethyl isoxazolines are widely studied, their monofluorinated analogs are extremely rare.[15] We envisioned that our recently developed technology involving fluoromethylene transfer from fluoromethyl sulfonium salts *via* an ylide to access 3-membered cycles-fluorocyclopropanes and fluoroepoxides,[8] could be adapted to access derivatives of monofluorinated isoxazolines to showcase formal [1 + 4] cyclization, yielding 5-membered heterocycles.

As a prominent class of isoxazoline derivatives, isoxazoline-*N*-oxides have gained broad interest from the perspective of their synthesis and application.[16]

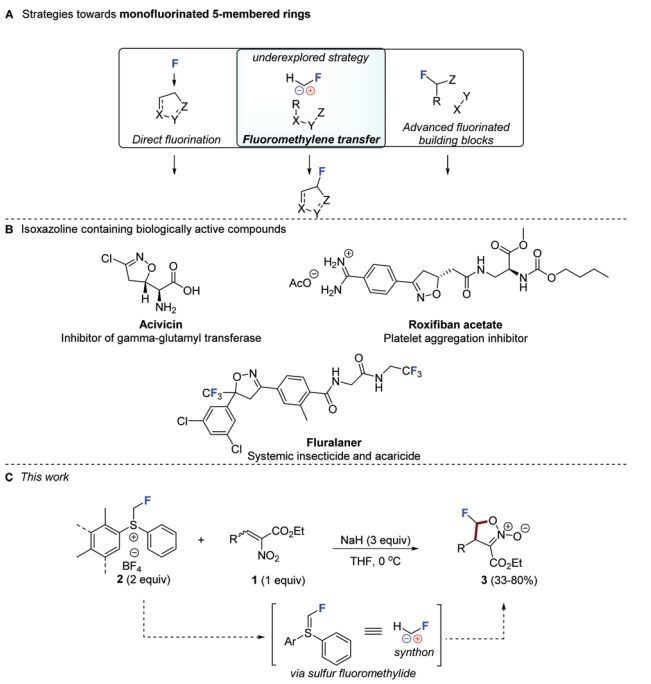


Fig. 1 (A) Strategies used to access monofluorinated five-membered heterocycles. (B) Biologically relevant compounds containing isoxazoline moieties. (C) Synthesis of 5-fluoro-isoxazoline-*N*-oxides by using a fluoromethylene transfer strategy.

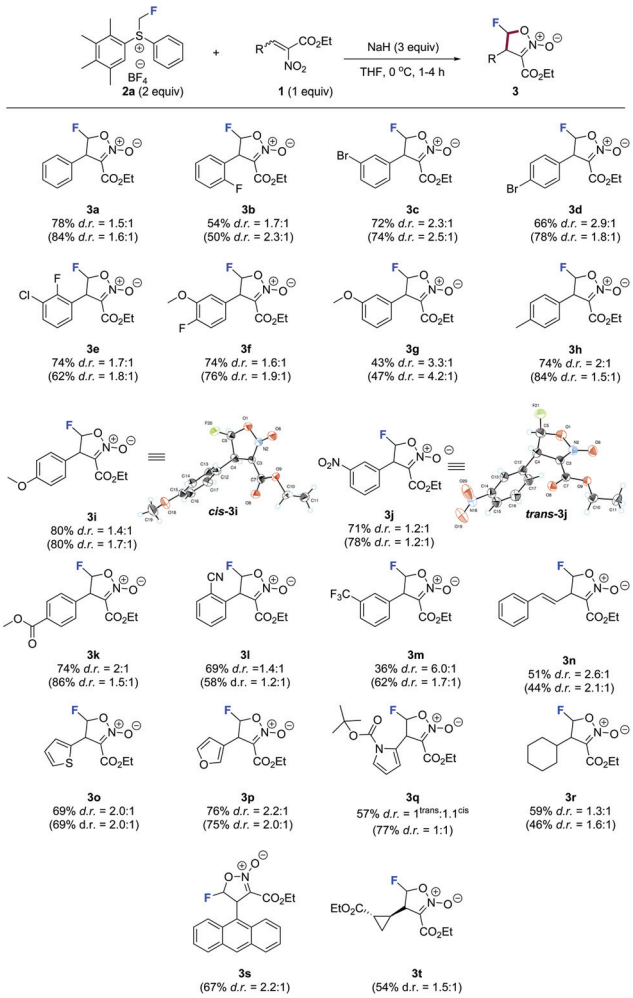
Latvian Institute of Organic Synthesis, Aizkraukles 21, LV-1006 Riga, Latvia.
E-mail: janis.veliks@osi.lv

†Electronic supplementary information (ESI) available. CCDC 2057602 and 2057603. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d1ob00270h

As a platform for the demonstration of 5-membered cycle formation by monofluoromethylene transfer, 2-nitroacrylates[17] were selected to afford previously unreported monofluorinated isoxazoline-*N*-oxides at the C5 position. Optimization studies were performed by using ethyl 2-nitro-3-phenylacrylate (**1a**) as a model substrate to form 3-(ethoxycarbonyl)-5-fluoro-4-phenyl-4,5-dihydroisoxazole *N*-oxide (**3a**) as the reaction product. Solvent screening (Table 1, entries 1–5) indicated that tetrahydrofuran is a superior reaction solvent. Sodium hydride turned out to be the most efficient base for the *in situ* generation of sulfur fluoromethylide that is to be trapped with nitroacrylate **1a** (entries 5, 7 and 8). 2,3,4,5-Tetramethylphenyl substituted sulfonium reagent **2a**[18] gave a slightly better yield; however, the simpler and affordable reagent **2b**[19] performance was comparable (entries 5 and 6). The optimal reaction conditions therefore consist of treating **1a** with **2a** (2 equiv) and sodium hydride (3 equiv) in anhydrous tetrahydrofuran at 0 °C giving the desired product **3a** in a good yield as a mixture of diastereomers (entry 5).

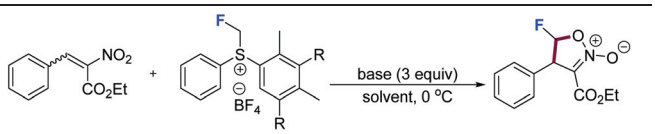
Under the optimized conditions (Table 1, entry 5), the substrate scope obtained by fluoromethylene transfer to nitroacrylates **1** was investigated (Scheme 1). The reaction conditions tolerate a large variety of arylidene nitro esters **1** bearing unsubstituted phenyl group **1a**, halogen substituents **1b–e**, electron donating groups **1f–i**, electron withdrawing groups **1j–m**, or substrates bearing conjugated vinyl-substituent **1n**, five-membered heterocycles **1o–q**, and alicyclic substrate **1r**. The corresponding isoxazoline-*N*-oxides **3** were obtained in moderate to very good yields. To our surprise, most of the products were chromatographically purifiable compounds with good to moderate stability. For all but **3l** and **3q**, the diastereomers could be easily separated. This is the first example of isolable[16n] monofluoro isoxazoline-*N*-oxides. The fluoromethylene transfer process is highly efficient; however, for less stable products (**3m**, **q**, **t**, and **s**) the lowered yield was determined by their partial decomposition upon isolation. In contrast to other nitroalkenes,[19] in the fluoromethylene transfer reaction of 2-nitroacrylates **1** using reagent **2a** the formation of fluorocyclopropanation products was not observed. The stereochemistry of both diastereomers was determined by comparison of the corresponding $^{3}J_{H(4)-H(5)}$ coupling constants in ^{1}H NMR spectra with estimated dihedral angles H–C(4)–C(5)–H for *trans*-**3a** (0 Hz and ~104° angle) and *cis*-**3a** (5.5 Hz and ~25° angle). This was further unambiguously supported by the X-ray structures of *cis*-**3i** and *trans*-**3j** isomers.

To test the scalability of the reaction, we performed an upscaled reaction for the [4 + 1] cyclization of nitroacrylate **1a**. For the upscaled reaction (Scheme 2), more affordable 2,4-



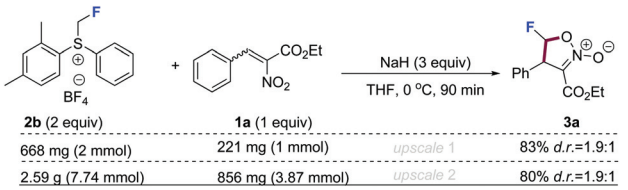
Scheme 1 Substrate scope of the formal [4 + 1] cyclization reaction. The reactions were performed under optimized reaction conditions on 0.1 to 0.2 mmol scale of **1**, see ESI† for more details. Isolated yields, unless otherwise stated. ^{1}H NMR yields in parentheses determined for crude product **3** before isolation. ^{1}H NMR yields determined by using EtOAc as the internal standard. dr determined from ^{1}H NMR of crude.

Table 1 Optimization of fluoromethylene transfer to 2-nitro-3-phenylacrylate (**1a**)



Entry[a]	Base	2	Solvent	Yield of **3a**, % [b]	dr *trans* : *cis*
1	NaH	**a**	MeCN	44	1.2 : 1
2	NaH	**a**	DMF	Traces	n.d.
3	NaH	**a**	1,4-Dioxane[d]	52	1.4 : 1
4	NaH	**a**	DCM	72	1.4 : 1
5[c]	**NaH**	**a**	**THF**	**82 (78)**	**1.6 : 1**
6[c]	NaH	**b**	THF	79	1.4 : 1
7	DBU	**a**	THF	0	—
8	LiHMDS[e]	**a**	THF[f]	8	1 : 1

[a] Reaction conditions: A base was added to a mixture of **1a** (0.0452 mmol) and **2** in a solvent (1.8 ml) under an Ar atmosphere at 0 °C. The reaction mixture was stirred at 0 °C, and the reaction progress was monitored by TLC. The crude reaction mixture was analyzed by ^{1}H NMR. [b] ^{1}H NMR yield determined using EtOAc as an internal reference. Isolated yield in parenthesis. [c] 0.109 mmol scale of **1a**. [d] RT. [e] −78 to 0 °C. [f] 1 M THF.

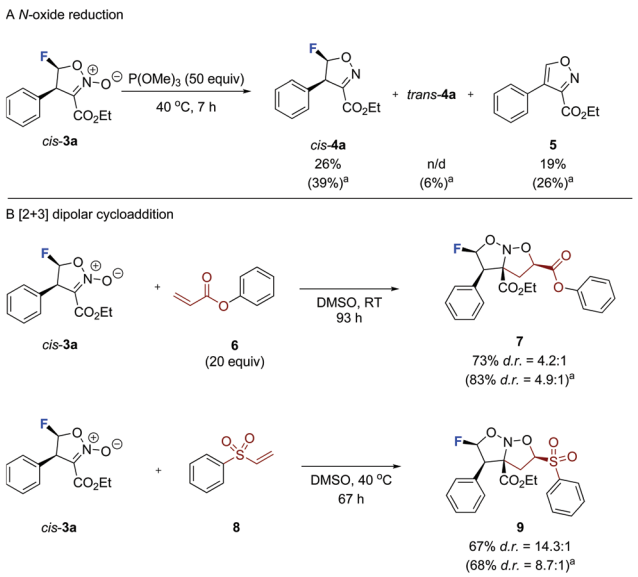


Scheme 2 Upscale of **3a** synthesis. Isolated yield dr determined from ^{1}H NMR spectra.

dimethyl-substituted fluoromethyl sulfonium salt **2b**[19] was used instead of tetramethyl reagent **2a**, giving access to the desired isoxazoline-*N*-oxides **3a** on the 0.2 g and 0.8 g scales with comparable yields to those reported in Scheme 1.

The corresponding *N*-oxide **3a** was reduced by using trimethyl phosphite[16h,k] to give isoxazole **4a**, albeit as a mixture of completely saturated isoxazoline **5**. Notably, performing the reaction with pure *cis*-**3a** we observed the formation of 6% *trans*-**4a** in addition to the major *cis*-**4a** product. This could be rationalized by the partial reversibility of HF elimination/addition for products **4** and **5**. Both reaction products **4** and **5** were separated by silica gel column chromatography (Scheme 3).

Furthermore, we investigated the possibility of performing the [3 + 2] dipolar cycloaddition of alkenes with *N*-oxide **3a**[16n] as a 1,3-dipole. The reaction proceeds well with terminal alkenes activated with electron-withdrawing groups, as exemplified on dipolarophiles such as phenyl acrylate (**6**) and phenyl vinylsulfone (**8**). The cycloaddition reaction proceeded smoothly in DMSO used as a reaction solvent at ambient temperature; however, full conversion was achieved in 3 to 4 days. The reaction proceeded with excellent regioselectivity and notable diastereoselectivity – out of 8 possible diastereomers, only two were detected. This demonstrates that our fluoromethylene transfer technology using fluoromethylide precursors **2a** and **2b** in combination with [3 + 2] dipolar cycloaddition can be used to reach high complexity monofluorinated products in just two steps.



Scheme 3 Functionalization of **3a**. Isolated yields reported (^{1}H NMR yields in parentheses, EtOAc as an internal standard).

In conclusion, we have demonstrated for the first time that fluoromethylene transfer from sulfonium reagents is a viable strategy that can be used for the construction of monofluorinated five-membered rings. Consequently, the synthetic methodology was developed to access monofluorinated isoxazoline-*N*-oxides as new monofluorinated scaffolds, which can be used for further modifications.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

Financial support was provided by the Latvian Council of Science project LZP-2019/1-0258. We acknowledge Prof. Dr Aigars Jirgensons for scientific advice and LIOS analytical service for NMR (Juris Popelis, Marina Petrova), MS (Solveiga Grinberga, Dace Hartmane, Valerija Krizanovska, Baiba Gukalova), X-ray crystallography (Sergey Belyakov) and elemental analysis (Emma Sarule).

Notes and references

1 (*a*) H. Mei, A. M. Remete, Y. Zou, H. Moriwaki, S. Fustero, L. Kiss, V. A. Soloshonok and J. Han, *Chin. Chem. Lett.*, 2020, **31**, 2401–2413; (*b*) H. Mei, J. Han, S. Fustero, M. Medio-Simon, D. M. Sedgwick, C. Santi, R. Ruzziconi and V. A. Soloshonok, *Chemistry*, 2019, **25**, 11797–11819.

2 (*a*) S. Preshlock, M. Tredwell and V. Gouverneur, *Chem. Rev.*, 2016, **116**, 719–766; (*b*) S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, *Chem. Soc. Rev.*, 2008, **37**, 320–330; (*c*) Y. Zhou, J. Wang, Z. Gu, S. Wang, W. Zhu, J. L. Aceña, V. A. Soloshonok, K. Izawa and H. Liu, *Chem. Rev.*, 2016, **116**, 422–518; (*d*) J. Wang, M. Sanchez-Rosello, J. L. Acena, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok and H. Liu, *Chem. Rev.*, 2014, **114**, 2432–2506.

3 Review on fluorine containing agrochemicals: T. Fujiwara and D. O'Hagan, *J. Fluorine Chem.*, 2014, **167**, 16–29.

4 R. Berger, G. Resnati, P. Metrangolo, E. Weber and J. Hulliger, *Chem. Soc. Rev.*, 2011, **40**, 3496–3508.

5 Syntheis of fluorinated 5-membered rings: (*a*) K. L. Kirk, *Fluorinated Five-Membered Nitrogen-Containing Heterocycles*, 2009; (*b*) Y. Shermolovich, *Fluorinated Five-Membered Heterocycles Containing Oxygen, Sulfur, Selenium, and Phosphorus*, 2009; (*c*) M. Baumann, I. R. Baxendale, S. V. Ley and N. Nikbin, *Beilstein J. Org. Chem.*, 2011, **7**, 442–495.

6 Representative examples of direct fluorination: (*a*) C. E. Stephens and J. A. Blake, *J. Fluorine Chem.*, 2004, **125**, 1939–1945; (*b*) P. J. Milner, Y. Yang and

S. L. Buchwald, *Organometallics*, 2015, **34**, 4775–4780; (*c*) V. Levchenko, Y. V. Dmytriv, A. V. Tymtsunik, K. Liubchak, A. Rudnichenko, A. V. Melnyk, S. Y. Veselovych, Y. V. Borodulin, O. M. Otsalyuk, A. A. Tolmachev and P. K. Mykhailiuk, *J. Org. Chem.*, 2018, **83**, 3265–3274.

7 Representative examples of building-block approach for the synthesis of 5-membered heterocycles: (*a*) N. K. Park, B. T. Kim, S. S. Moon, S. L. Jeon and I. H. Jeong, *Tetrahedron*, 2004, **60**, 7943–7949; (*b*) C. L. Bumgardner and J. C. Sloop, *J. Fluorine Chem.*, 1992, **56**, 141–146.

8 (*a*) R. Melngaile, A. Sperga, K. K. Baldridge and J. Veliks, *Org. Lett.*, 2019, **21**, 7174–7178; (*b*) J. Veliks and A. Kazia, *Chemistry*, 2019, **25**, 3786–3789; (*c*) A. Kazia, R. Melngaile, A. Mishnev and J. Veliks, *Org. Biomol. Chem.*, 2020, **18**, 1384–1388; (*d*) J. Veliks, M. Videja, A. Kinens, R. Bobrovs, M. Priede and J. Kuka, *ACS Med. Chem. Lett.*, 2020, **11**, 2146–2150.

9 (*a*) X. Song, J. Chang, D. Zhu, J. Li, C. Xu, Q. Liu and M. Wang, *Org. Lett.*, 2015, **17**, 1712–1715; (*b*) Q. Liu, X. Shen, C. Ni and J. Hu, *Angew. Chem., Int. Ed.*, 2017, **56**, 619–623; (*c*) D. G. Cox, N. Gurusamy and D. J. Burton, *J. Am. Chem. Soc.*, 1985, **107**, 2811–2812; (*d*) J. H. van Steenis and A. van der Gen, *Eur. J. Org. Chem.*, 2001, 897–910; (*e*) L. Zhu, C. Ni, Y. Zhao and J. Hu, *Tetrahedron*, 2010, **66**, 5089–5100; (*f*) G. K. S. Prakash, A. Shakhmin, M. Zibinsky, I. Ledneczki, S. Chacko and G. A. Olah, *J. Fluorine Chem.*, 2010, **131**, 1192–1197.

10 Review on 3-membered fluorinated rings: (*a*) J. Decaens, S. Couve-Bonnaire, A. Charette, T. Poisson and P. Jubault, *Chemistry*, 2020, **27**, 2935–2962. Selected examples for the synthesis of 3-membered rings by fluoromethylene transfer: (*b*) M. Schlosser and G. Heinz, *Angew. Chem., Int. Ed. Engl.*, 1968, **7**, 820–821; (*c*) J. L. Hahnfeld and D. J. Burton, *Tetrahedron Lett.*, 1975, **16**, 1819–1822; (*d*) L. P. Beaulieu, J. F. Schneider and A. B. Charette, *J. Am. Chem. Soc.*, 2013, **135**, 7819–7822; (*e*) X. Shen, W. Zhang, L. Zhang, T. Luo, X. Wan, Y. Gu and J. Hu, *Angew. Chem., Int. Ed.*, 2012, **51**, 6966–6970; (*f*) S. Monticelli, M. Colella, V. Pillari, A. Tota, T. Langer, W. Holzer, L. Degennaro, R. Luisi and V. Pace, *Org. Lett.*, 2019, **21**, 584–588; (*g*) M. Colella, A. Tota, A. Grossjohann, C. Carlucci, A. Aramini, N. S. Sheikh, L. Degennaro and R. Luisi, *Chem. Commun.*, 2019, **55**, 8430–8433; (*h*) A. S. Konev, M. S. Novikov and A. F. Khlebnikov, *Russ. J. Org. Chem.*, 2007, **43**, 286–296.

11 A. Sysak and B. Obminska-Mrukowicz, *Eur. J. Med. Chem.*, 2017, **137**, 292–309.

12 E. Vitaku, D. T. Smith and J. T. Njardarson, *J. Med. Chem.*, 2014, **57**, 10257–10274.

13 (*a*) S. Minakata, S. Okumura, T. Nagamachi and Y. Takeda, *Org. Lett.*, 2011, **13**, 2966–2969; (*b*) A. Yoshimura, K. R. Middleton, A. D. Todora, B. J. Kastern, S. R. Koski, A. V. Maskaev and V. V. Zhdankin, *Org. Lett.*, 2013, **15**, 4010–4013; (*c*) A. P. Kozikowski, *Acc. Chem. Res.*, 1984, **17**, 410–416.

14 For acivicin, see: (*a*) L. Allen, R. Meck and A. Yunis, *Res. Commun. Chem. Pathol. Pharmacol.*, 1980, **27**, 175–182 For roxifiban acetate, see: (*b*) J. Murphy, R. S. Wright, I. Gussak, B. Williams, R. N. Daly, V. A. Cain, H. J. Pieniaszek, S. K. Sy, W. Ebling, K. Simonson, R. A. Wilcox and S. L. Kopecky, *Am. J. Cardiovasc. Drugs*, 2003, **3**, 101–112 For fluralaner, see: (*c*) F. M. Walther, M. J. Allan, R. K. A. Roepke and M. C. Nuernberger, *Parasit. Vectors*, 2014, **7**, 87.

15 V. Kumar and K. Kaur, *J. Fluorine Chem.*, 2015, **180**, 55–97.

16 For review on chemistry of nitronates, see: (*a*) A. Tabolin, A. Sukhorukov, S. Ioffe and A. Dilman, *Synthesis*, 2017, 3255–3268 Selected examples for the synthesis of isoxazoline-*N*-oxides: (*b*) H. Lin, Q. Shen and L. Lu, *J. Org. Chem.*, 2011, **76**, 7359–7369; (*c*) C. D. Schmidt, J. Kaschel, T. F. Schneider, D. Kratzert, D. Stalke and D. B. Werz, *Org. Lett.*, 2013, **15**, 6098–6101; (*d*) E. Marotta, L. M. Micheloni, N. Scardovi and P. Righi, *Org. Lett.*, 2001, **3**, 727–729; (*e*) G. Rosini, R. Galarini, E. Marotta and P. Righi, *J. Org. Chem.*, 1990, **55**, 781–783; (*f*) T. Sandmeier, F. W. Goetzke, S. Krautwald and E. M. Carreira, *J. Am. Chem. Soc.*, 2019, **141**, 12212–12218; (*g*) S. Zen, E. Kaji and K. Takahashi, *Nippon Kagaku Kaishi*, 1986, 55–59; (*h*) Z. Shi, B. Tan, W. W. Y. Leong, X. Zeng, M. Lu and G. Zhong, *Org. Lett.*, 2010, **12**, 5402–5405; (*i*) T. Sakakibara and R. Sudoh, *J. Chem. Soc., Chem. Commun.*, 1977, 7–8; (*j*) M. Clagett, A. Gooch, P. Graham, N. Holy, B. Mains and J. Strunk, *J. Org. Chem.*, 1976, **41**, 4033–4035; (*k*) C.-Y. Zhu, X.-L. Sun, X.-M. Deng, J.-C. Zheng and Y. Tang, *Tetrahedron*, 2008, **64**, 5583–5589; (*l*) N. B. Chernysheva, A. S. Maksimenko, F. A. Andreyanov, V. P. Kislyi, Y. A. Strelenko, V. N. Khrustalev, M. N. Semenova and V. V. Semenov, *Tetrahedron*, 2017, **73**, 6728–6735; (*m*) S. Zen and M. Koyama, *Bull. Chem. Soc. Jpn.*, 1971, **44**, 2882–2882; (*n*) V. A. Motornov, A. A. Tabolin, R. A. Novikov, Y. V. Nelyubina, V. G. Nenajdenko and S. L. Ioffe, *Org. Chem. Front.*, 2018, **5**, 2588–2594.

17 J. F. Briones and G. S. Basarab, *Chem. Commun.*, 2016, **52**, 8541–8544.

18 G. K. Prakash, I. Ledneczki, S. Chacko and G. A. Olah, *Org. Lett.*, 2008, **10**, 557–560.

19 A. Sperga, E. Melngaile, A. Kazia, S. Belyakov and J. Veliks, *J. Org. Chem.*, 2021, **86**, 3196–3212.