

RESEARCH ARTICLE

View Article Online
View Journal | View IssueCite this: *Org. Chem. Front.*, 2018, 5, 226Received 9th August 2017,
Accepted 27th September 2017

DOI: 10.1039/c7qo00705a

rsc.li/frontiers-organic

Calcium-mediated one-pot preparation of isoxazoles with deuterium incorporation†

Maria S. Ledovskaya,^a Konstantin S. Rodygin^a and Valentine P. Ananikov  *^{a,b}

In this work, a novel synthetic methodology for the one-pot preparation of isoxazoles directly from the reaction of calcium carbide with aldoximes is reported. Calcium carbide acts as a safe and inexpensive acetylene source and, in addition, as a source of the Ca(OH)₂ base to enable the generation of nitrile oxide. Various 3-substituted isoxazoles were synthesized from the corresponding aldoximes in good yields (up to 95%) and a series of new deuterated 4,5-dideuteroisoxazoles were prepared.

Introduction

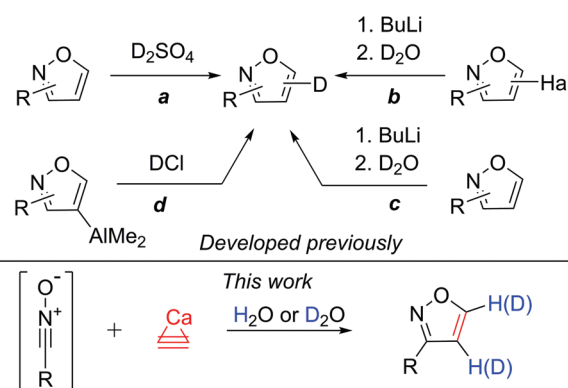
The covalent carbon–deuterium (C–D) bond is noticeably stronger compared to a carbon–hydrogen (C–H) bond. This difference in the bond strength opens many practical opportunities. For example, comparison of the C–H bond and C–D bond reactivity may be used in the study of reaction mechanisms.¹ In addition to mechanistic studies, deuterated starting materials can be applied to alter the reaction selectivities in total syntheses. This approach has been utilized in the synthesis of pharmaceutical substances.² Recently, deuterium substitution led to a very interesting application with the enhancement of the metabolic stability of drugs. The larger strength of the C–D bond in deuterated pharmaceutical substances leads to a higher effectiveness and lower toxicity in comparison with those of the undeuterated analogs.³ In view of the recent advances in this field,⁴ the synthesis of new deuterated substances is a demanded goal for organic and pharmaceutical chemistry.

Heterocyclic molecules possess a diverse range of biological activities and are ubiquitously used in many drugs.^{3–5} Undoubtedly, the deuteration of heterocyclic cores is a demanded research area to develop a new generation of drugs. Isoxazoles demonstrate a wide range of biological activities and are used in drug development.⁶ However, all the methods used previously to obtain deuterated isoxazoles had severe limitations. In particular, deuterium sulfate or deuterium chloride was used to introduce deuterium into the isoxazole

ring. Using this procedure, the starting isoxazole was treated under harsh conditions with acidic reagents to obtain 4- or 5-deuteroisoxazoles (Scheme 1, path a).⁷ This approach has rather limited functional group tolerance.

The other way to yield 4- or 5-deuteroisoxazoles is the sequential treatment of 4- and 5-halogenated isoxazoles with butyl lithium and deuterium oxide (Scheme 1, path b).⁸ Additionally, 4- or 5-deuteroisoxazoles can be obtained by lithium-mediated H–D exchange (Scheme 1, path c).^{1a,b} The application of BuLi as a reagent imposes even more difficulties with regard to the functional group tolerance. Highly air- and moisture-sensitive aluminated isoxazoles can be used to prepare 4-deuteroisoxazoles by reaction with DCl under glove-box conditions (Scheme 1, path d).⁹ A few other approaches to deuteroisoxazoles have also been reported.¹⁰

In this work, we propose a novel synthetic approach to prepare isoxazoles with the facile ability for deuterium incorporation. This methodology is based on a 1,3-dipolar cycloaddition of nitrile oxide to acetylene or deuterioacetylene gen-



Scheme 1 Known deuteration via the substitution reaction and the developed atom-economical route via cycloaddition.

^aSaint Petersburg State University, Universitetsky prospect 26, Peterhof, 198504, Russia

^bN. D. Zelinsky Institute of Organic Chemistry Russian Academy of Sciences, Leninsky prospect 47, Moscow, 119991, Russia. E-mail: val@ioc.ac.ru

† Electronic supplementary information (ESI) available. CCDC 1541266. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c7qo00705a



erated *in situ* (Scheme 1). Here, calcium carbide acts as a safe and readily available acetylene source.¹¹ Nitrile oxide is generated from the corresponding chloroaloximes in the presence of a base.¹² Chloroaloximes can be easily synthesized by aldoxime chlorination with chlorine,¹³ *N*-chlorosuccinimide (NCS)¹⁴ or other reagents.¹⁵

Results and discussion

As a model process, the reaction of 4-tolualdehyde oxime **1a** and chlorinated derivative **2a** with calcium carbide was chosen. To test the proposed utilization of calcium carbide as an acetylene source, we first studied the sequential transformation (Table 1). Compound **2a** was synthesized from **1a** and isolated, followed by a series of experiments utilizing **2a** as a starting material. First, we tested various solvents (entries 1–6, Table 1) and obtained the best result with carbon tetrachloride (entry 6, Table 1). Using triethylamine and pyridine as bases gave the same yields (entries 6 and 7, Table 1).

Surprisingly, Ca(OH)₂ formed *in situ* upon reaction of CaC₂ with water was an excellent base in this process, and the resulting isoxazole was formed in 82% yield without the addition of any extra base (entry 8, Table 1). The variation in the amount of calcium carbide revealed that 2 mmol was a suitable value (entries 8–10, Table 1). It should be noted that the reaction proceeded in a good yield using 1 mmol of calcium carbide

(entry 10, Table 1), however an excess of this reagent improved the selectivity by suppressing the side-reactions. Taking into account the very low price of calcium carbide and the nontoxic nature of generated calcium hydroxide, the usage of an excess of calcium carbide is the synthetic procedure of choice for carrying out the reaction.

Next, we addressed the possibility of a one-pot reaction to synthesize **4a** directly from **1a** (entry 11, Table 1). For this transformation *N*-chlorosuccinimide was used to generate **2a** *in situ*. The yield in the one-pot reaction of **1a** with NCS and calcium carbide was identical compared to that of the corresponding sequential process (entries 11 and 8, Table 1). The application of Ca(OH)₂ as a base was confirmed for the one-pot reaction as well, where the addition of an extra base did not change the product yield (entries 11 and 12, Table 1).

With the optimized conditions in hand, the substrate scope with a variety of aldoximes was explored (Table 2). The reaction worked well for a wide range of substrates with various func-

Table 1 Optimization of the reaction conditions^a

Entry	Substrate	Solvent	Base	Yield, %
1	2a	DMSO	Et ₃ N	28
2	2a	Et ₂ O	Et ₃ N	40
3	2a	Benzene	Et ₃ N	81
4	2a	CH ₂ Cl ₂	Et ₃ N	77
5	2a	CHCl ₃	Et ₃ N	75
6	2a	CCl ₄	Et ₃ N	82
7	2a	CCl ₄	Py	81
8	2a	CCl ₄	—	82
9 ^b	2a	CCl ₄	—	80
10 ^c	2a	CCl ₄	—	66
11	1a	CCl ₄	—	82
12	1a	CCl ₄	Et ₃ N	82
13	1a	CCl ₄	Py	80

^a Reaction conditions: **1a** or **2a** (0.3 mmol), CaC₂ (2.0 mmol), H₂O (4.0 mmol), *N*-chlorosuccinimide (0.4 mmol, for reactions with **1a**), base (0.3 mmol), solvent (1.5 ml), 20 °C, 48 h; yields determined by NMR. ^b 3.0 mmol of CaC₂ and 6.0 mmol of H₂O were used. ^c 1.0 mmol of CaC₂ and 2.0 mmol of H₂O were used.

Table 2 One-pot reaction of aldoximes with CaC₂ and NCS^{a,b}

Reaction	Substrate	Yield (%)	Isolated Yield (%)
Sequential transformation	2a (p-Tol)	82%	81%
	2b (t-Bu)	95%	95%
	2c (H ₃ CO)	91%	88%
	2d (H ₃ CO)	60%	59%
	2e (H ₃ CO)	92%	90%
One-pot reaction	1a (p-Tol)	82%	81%
	1b (Ph)	84%	77%
	1c (I)	95%	95%
	1d (Br)	93%	92%
	1e (Br)	75%	71%
	1f (Br)	87%	84%
	1g (Cl)	75%	72%
	1h (F)	53%	47%
	1i (F)	83%	78%
	1j (NO ₂)	53%	50%
	1k (NO ₂)	72%	72%
	1l (H ₃ C ₂ N)	63%	63%
	1m (AcHN)	44%	44%
	1n (OMe)	86%	86%
	1o (OMe)	56%	53%
	1p (Cl)	93%	93%
	1q (Cl)	94%	94%
	1r (Br)	67%	61%
	1s (OMe, OEt)	62%	60%
	1t (Ph)	88%	85%
1u (Bicyclic)	82%	81%	

^a Reaction conditions: Aldoxime **1** (0.3 mmol), CaC₂ (2.0 mmol), H₂O (4.0 mmol), *N*-chlorosuccinimide (0.4 mmol), CCl₄ (1.5 ml), 20 °C, 48 h. ^b The yields were determined by NMR, and the isolated yields are given in parentheses. ^c A 1:1 benzene-dichloromethane mixture was used as a solvent.

tional groups, affording the desired isoxazoles in moderate to excellent yields. The highest yields were observed for the reactions of calcium carbide with **1b** (95% yield), **1c** and **1e** (91% and 92% yields), *ortho*-iodo- (**1g**) and *ortho*-bromo- (**1h**) derivatives (95% and 93% yields), **1t** and **1u** (93% and 94% yields). Benzaldoxime **1f** gave **4f** in good yield (84%), and aldoximes **1a**, **1i–1k**, **1m**, **1o**, and **1r** also provided good yields (72–87%). Anthracene derivative **1x** and substrate **1y** derived from (1*R*)-(-)-myrtenal gave the desired isoxazoles in good yields (88% and 82%, respectively). Overall, a facile transformation was developed for the preparation of many products (Table 2).

Moderate yields of nitro-, dimethylamino- and acetamido-derived products **4n–4q** were related to the poor solubility of the starting materials in the organic solvent. For the synthesis of **4p** and **4q**, we tested other solvents (CH₂Cl₂, CHCl₃, CCl₄, benzene, C₆H₆–CH₂Cl₂, and CCl₄–EtOAc), and a C₆H₆–CH₂Cl₂ mixture provided better isolated product yields of 63% and 44%, respectively.

For additional characterization, product **4z** was synthesized and the structure was established by X-ray analysis (see the ESI†).


The application of calcium carbide provides an excellent possibility for deuterium incorporation. Deuterated acetylene C₂D₂ was generated by the reaction of CaC₂ with D₂O. The optimization of the deuteration procedure involving varying the amounts of D₂O and the reagents, as well as changing the reaction conditions, was carried out (entries 1–8, Table 3).¹⁶ As a result, an excellent overall deuterium incorporation of 98% was observed under the optimized conditions (entry 9, Table 3).

Table 3 Optimization of the reaction of 2,6-dichlorobenzaldoxime with CaC₂, D₂O and NCS^a

Entry	D ₂ O (mmol)	Product distribution			Deuterium incorporation ^c , %
		5 ^b , %	5' + 5'' ^b , %	4 ^b , %	
1	2	80	18	2	89
2	4	82	16	2	90
3	8	86	12	2	92
4	10	82	16	2	90
5	8 ^d	75	22	3	86
6	8 ^e	86	12	2	92
7	8 ^f	89	10	1	94
8	8 ^{f,g}	92	7	1	96
9	8 ^h	96	4	Trace	98

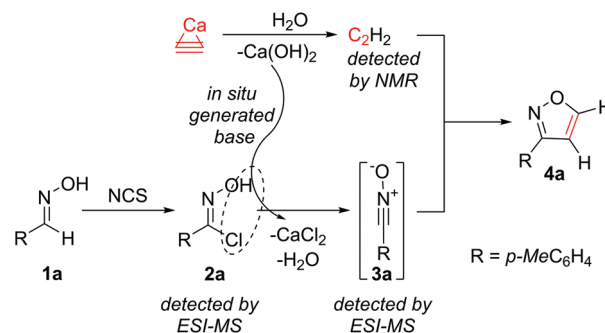
^a Reaction conditions: Aldoxime **1u** (R = 2,6-Cl₂C₆H₃, 0.3 mmol), CaC₂ (2.0 mmol), D₂O (4.0 mmol), *N*-chlorosuccinimide (0.4 mmol), CCl₄ (1.5 ml), 20 °C, 48 h. ^b Determined by NMR according to the intensity of the residual ¹H signals. ^c Overall deuterium incorporation into products = 5 + (5' + 5'')/2. ^d The two-step sequence with succinimide removal. ^e The starting oxime was treated with D₂O before the reaction with CaC₂. ^f The starting oxime was treated with a D₂O–CDCl₃ mixture. ^g 1.5 mmol of CaC₂ was used. ^h Starting aldoxime (0.25 mmol) and NCS (0.3 mmol), with all other parameters the same as in entry 8.

Table 4 Synthesis of deuterated isoxazoles (see Table 3 for reaction and description)

Entry	R	Yield of 5 , %	Deuterium incorporation ^a , %
1	4-MeC ₆ H ₄	82	98
2	2-MeOC ₆ H ₄	91	98
3	3-MeOC ₆ H ₄	60	96
4	4-MeOC ₆ H ₄	92	96
5	Ph	84	94
6	2-IC ₆ H ₄	95	98
7	2-BrC ₆ H ₄	93	98
8	3-BrC ₆ H ₄	75	96
9	4-BrC ₆ H ₄	87	98
10	4-ClC ₆ H ₄	75	98
11	3-FC ₆ H ₄	53	96
12	4-FC ₆ H ₄	83	98
13	2,3-(MeO) ₂ C ₆ H ₃	86	97
14	3,4-(MeO) ₂ C ₆ H ₃	56	98
15	2,4-Cl ₂ C ₆ H ₃	93	97
16	2,6-Cl ₂ C ₆ H ₃	94	98
17	Anthracene-9-yl	88	97
18		82	97

Using these optimized conditions, the deuteration process was studied for different products (Table 4). In most cases, ≥97% deuterium incorporation was observed. In only a few cases, 94–96% overall deuterium incorporation in the 4- and 5-positions of the isoxazoles was found, which nevertheless are also high-performance deuteration processes (Table 4). Synthesized 4,5-dideuterioisoxazoles **5** were stable compounds and were easily isolated by standard procedures. Purification on silica was performed without a change in the deuteration purity (see the ESI†).

It was of much interest to investigate the reaction mechanism. First, the key role of calcium hydroxide formed *in situ* was studied (Scheme 2). Two reactions were carried out using a solution saturated with acetylene gas (an external source of acetylene gas was used without the addition of CaC₂). To one reaction, the corresponding amount of Ca(OH)₂ was added, and both reactions were conducted under the same conditions at 20 °C for 48 h. Indeed, product formation was observed only in the presence of Ca(OH)₂.



Scheme 2 Proposed mechanism of isoxazole formation.



The generation of acetylene in the studied system was confirmed by NMR (Scheme 2). Reaction monitoring with electro-spray ionization mass-spectrometry (ESI-MS) helps in detecting the corresponding peaks for chloroaldoxime **2a** ($m/z = 170.0369$ $[M + H]^+$) and nitrile oxide **3a** ($m/z = 156.0416$, $[M + Na]^+$). The advantage of the developed procedure was the controlled reaction of calcium carbide with water, thus gradually releasing gaseous acetylene and calcium hydroxide. A small concentration of reactive intermediate **3a** provided reliable conditions for the reaction of interest and avoided side reactions.

Conclusions

To summarize, a simple procedure for the preparation of 3-substituted isoxazoles and novel 4,5-dideuterioisoxazoles was developed. This procedure was based on the reaction of readily available aldoximes and *N*-chlorosuccinimide with calcium carbide. Calcium carbide acted as a safe and inexpensive source of acetylene (C_2H_2 and C_2D_2) and provided $Ca(OH)_2$ to mediate the reaction. A nontoxic inorganic salt, $CaCl_2$, was released at the end of the reaction, and the products were easily separated. The replacement of acetylene with CaC_2 allowed for the use of standard laboratory equipment (without complicated equipment for high-pressure acetylene) and for the easy incorporation of deuterium.

A combination of CaC_2 and D_2O is an attractive option for deuterium incorporation *via* atom-economical cycloaddition reactions involving C_2D_2 . Deuterium labeling *via* cycloaddition has valuable advantages compared to substitution reactions, which are not atom economical and possess poor functional group tolerance. The studied route for *in situ* C_2D_2 generation has a valuable advantage in terms of not only a convenient experimental procedure, but also cost-efficiency (C_2D_2 gas in balloons is highly expensive). We anticipate that the application of this protocol will provide access to other valuable heterocyclic and labelled molecules.

Experimental

General procedure for the synthesis of aldoximes **1**

To a round-bottom flask equipped with a magnetic stir bar, 0.02 mol of the corresponding aldehyde and 0.022 mol of hydroxylamine hydrochloride were added. Then, 15 ml of ethanol and 5 ml of water were added, followed by 0.015 mol of sodium carbonate (added in one portion). The resulting mixture was stirred at room temperature for 24 hours. Then, the solvent was evaporated, and the residue was washed with water to remove inorganics and recrystallized from the appropriate solvent.

Sequential reactions for the synthesis of 3-substituted isoxazoles **4** from chloroaldoximes and calcium carbide

The corresponding chloroaldoximes were synthesized by the procedure reported previously.¹⁷ A reaction tube was loaded

with chloroaldoxime (0.3 mmol) and calcium carbide (2 mmol). Then, 1.5 ml of CCl_4 (or toluene) was added, the resulting mixture was stirred until a suspension formed, and deionized water (4 mmol) was added. The reaction tube was immediately sealed, and the mixture was stirred at room temperature for 48 hours. After the reaction mixture was filtered, the solid residue was additionally extracted with chloroform. All organics were combined, and the solvent was removed using a rotary evaporator. Then, the product was purified by chromatography (hexane–ethyl acetate as an eluent).

One-pot reaction for the synthesis of 3-substituted isoxazoles **4** from aldoximes and calcium carbide

A reaction tube was loaded with an aldoxime (0.3 mmol), calcium carbide (2 mmol) and 0.4 mmol of *N*-chlorosuccinimide. Then, 1.5 ml of CCl_4 was added, the resulting solution was stirred until the oxime dissolved, and then deionized water (4 mmol) was added. The reaction tube was immediately sealed, and the mixture was stirred at room temperature for 48 hours. After the reaction mixture was filtered, the solid residue was additionally washed with chloroform. All organics were combined, and the solvent was removed using a rotary evaporator. Then, the product was purified by chromatography (hexane–ethyl acetate as an eluent).

General procedure for the synthesis of 4,5-dideuterioisoxazoles **5**

All manipulations were carried out under an argon atmosphere. Anhydrous reagents and solvents were used. $CDCl_3$ was treated with Al_2O_3 to avoid aldoxime *E-Z* isomerization in $CDCl_3$ and was dried over molecular sieves to avoid D-H exchange with the water contaminants in chloroform.

A reaction tube equipped with a magnetic stir bar was loaded with the aldoxime (100 mg), 0.75 ml of $CDCl_3$ and 1.0 ml of D_2O . The tube was sealed, and the mixture was stirred at 37 °C for 120 hours. Then, the organic layer was separated, and the solvent was evaporated. The resulting *O*-deuterated oxime was immediately used in the next step.

A reaction tube was loaded with *D*-aldoxime (0.25 mmol), calcium carbide (1.5 mmol) and 0.3 mmol of *N*-chlorosuccinimide. Then, 1.5 ml of CCl_4 was added, the resulting solution was stirred until the oxime dissolved, and then D_2O (8 mmol) was added. The reaction tube was immediately sealed, and the mixture was stirred at room temperature for 48 hours. After the reaction mixture was filtered, the solid residue was additionally washed with a small portion of chloroform. All organics were combined, and the solvent was removed using a rotary evaporator. Then, the product was purified by chromatography (hexane–ethyl acetate as an eluent).

Conflicts of interest

There are no conflicts to declare.



Acknowledgements

We gratefully acknowledge the financial support from the Russian Science Foundation (Project No 16-13-10301). This research made use of resources from the X-ray Diffraction Centre, Centre for Magnetic Resonance, Educational Resource Center of Chemistry and the Centre for Chemical Analysis and Materials of Saint-Petersburg State University.

Notes and references

- (a) M. Shigenobu, K. Takenaka and H. Sasai, *Angew. Chem., Int. Ed.*, 2015, **54**, 9572; (b) J.-H. Chu, C.-C. Chen and M.-J. Wu, *Organometallics*, 2008, **27**, 5173; (c) T. K. Goncharov, V. V. Dubikhin, E. L. Ignat'eva and G. M. Nazin, *Russ. J. Phys. Chem. B*, 2015, **9**, 695.
- M. Miyashita, M. Sasaki, I. Hattori, M. Sakai and K. Tanino, *Science*, 2004, **305**, 495.
- (a) D. J. Kushner, A. Baker and T. G. Dunstall, *Can. J. Physiol. Pharmacol.*, 1999, **77**, 79; (b) S. L. Harbeson and R. D. Tung, *Annu. Rep. Med. Chem.*, 2011, **46**, 403; (c) N. A. Meanwell, *J. Med. Chem.*, 2011, **54**, 2529; (d) D. H. Phillips, G. A. Potter, M. N. Horton, A. Hewer, C. Crofton-Sleigh, M. Jarman and S. Venitt, *Carcinogenesis*, 1994, **15**, 1487; (e) M. Jarman, G. K. Poon, M. G. Rowlands, R. M. Grimshaw, M. N. Horton, G. A. Potter and R. McCague, *Carcinogenesis*, 1995, **16**, 683; (f) A. E. Mutlib, R. J. Gerson, P. C. Meunier, P. J. Haley, H. Chen, L. S. Gan, M. H. Davies, B. Gemzik and D. D. Christ, *Toxicol. Appl. Pharmacol.*, 2000, **169**, 102.
- (a) A. Katsnelson, *Nat. Med.*, 2013, **19**, 656; (b) F. Maltais, Y. C. Jung, M. Chen, J. Tanoury, R. B. Perni, N. Mani, L. Laitinen, H. Huang, S. Liao, H. Gao, D. F. Krahn, J. A. Markwalder, S. P. Seitz, R. T. Robertson and G. T. Miwa, *J. Med. Chem.*, 2009, **52**, 7993; (c) A. Mullard, *Nat. Rev. Drug Discovery*, 2017, **16**, 305.
- The Chemistry of Heterocyclic Compounds*, ed. A. Padwa and W. H. Pearson, 2002, vol. 59.
- (a) A. J. Wilensky, P. N. Friel, L. M. Ojemann, C. B. Dodrill, K. B. McCormick and R. H. Levy, *Epilepsia*, 1985, **26**, 212; (b) H.-W. Chan, C.-Y. Huang, W.-J. Feng and Y.-C. Yen, *J. Affective Disord.*, 2016, **205**, 360; (c) F. Fang, H. Sun, Z. Wang, M. Ren, J. R. Calabrese and K. Gao, *CNS Drugs*, 2016, **30**, 845; (d) A. Prakash and B. Jarvis, *Drugs*, 1999, **58**, 1137; (e) A. C. Bowen, S. Y. C. Tong, R. M. Andrews, I. M. O'Meara, M. I. McDonald, M. D. Chatfield, B. J. Currie and J. R. Carapetis, *Lancet*, 2014, **384**, 2132; (f) B. Negi, D. Kumar, W. Kumbukgolla, S. Jayaweera, P. Ponnann, R. Singh, S. Agarwal and D. S. Rawat, *Eur. J. Med. Chem.*, 2016, **115**, 426; (g) K. A. M. Attia, M. W. I. Nassar, M. B. El-Zeiny and A. Serag, *Spectrochim. Acta, Part A*, 2016, **161**, 64; (h) J.-M. Dogné, C. T. Supuran and D. Pratico, *J. Med. Chem.*, 2005, **48**, 2251.
- (a) H. G. Leis, G. Fauler and W. Winischhofer, *Curr. Org. Chem.*, 1998, **2**, 131; (b) A. G. Burton, P. P. Forsythe, C. D. Johnson and A. R. Katritzky, *J. Chem. Soc. B*, 1971, 2365.
- J. H. Bowie, R. K. M. R. Kallury and R. G. Cooks, *Aust. J. Chem.*, 1969, **22**, 563.
- O. Jackowski, T. Lecourt and L. Micouin, *Org. Lett.*, 2011, **13**, 5664.
- (a) P. Allegretti and E. M. Ferreira, *Chem. Sci.*, 2013, **4**, 1053; (b) S. E. Lowe and J. Sheridan, *Chem. Phys. Lett.*, 1978, **58**, 79.
- (a) K. S. Rodygin, G. Werner, F. A. Kucherov and V. P. Ananikov, *Chem. – Asian J.*, 2016, **11**, 965; (b) R. Mataka, Y. Adachia and H. Matsubara, *Green Chem.*, 2016, **18**, 2614; (c) E. Rattanangkool, T. Vilaivan, M. Sukwattanasinitt and S. Wacharasindhu, *Eur. J. Org. Chem.*, 2016, 4347; (d) K. S. Rodygin and V. P. Ananikov, *Green Chem.*, 2016, **18**, 482; (e) K. S. Rodygin, A. A. Kostin and V. P. Ananikov, *Mendeleev Commun.*, 2015, **25**, 415; (f) G. Werner, K. S. Rodygin, A. A. Kostin, E. G. Gordeev, A. S. Kashin and V. P. Ananikov, *Green Chem.*, 2017, **19**, 3032; (g) A. Hosseini, D. Seidel, A. Miska and P. R. Schreiner, *Org. Lett.*, 2015, **17**, 2808; (h) R. Mataka, Y. Niwa and H. Matsubara, *Org. Lett.*, 2015, **17**, 2354; (i) N. Kaewchangwat, R. Sukato, V. Vchirawongkwin, T. Vilaivan, M. Sukwattanasinitt and S. Wacharasindhu, *Green Chem.*, 2015, **17**, 460.
- (a) L. I. Belen'kii, *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis: Novel Strategies in Synthesis*, ed. H. Feuer, Wiley, 2nd edn, 2008, pp. 1–128; (b) F. Heaney, *Eur. J. Org. Chem.*, 2012, 3043; (c) L. Jiang, T. Gao, Z. Li, S. Sun, C. Kim, C. Huang, H. Guo, J. Wang and Y. Xing, *Tetrahedron Lett.*, 2016, **57**, 712; (d) N. C. Tran, H. Dhondt, M. Flipo, B. Deprez and N. Willand, *Tetrahedron Lett.*, 2015, **56**, 4119; (e) S. Grecian and V. V. Fokin, *Angew. Chem., Int. Ed.*, 2008, **47**, 8285; (f) J. E. Grob, J. Nunez, M. A. Dechantsreiter and L. G. Hamann, *J. Org. Chem.*, 2011, **76**, 10241.
- (a) M. J. Kohl and R. G. Lejeune, *Steroids*, 2002, **67**, 71; (b) O. V. Demina, A. A. Khodonov, E. I. Sinauridze, V. I. Shvets and S. D. Varfolomeeva, *Russ. Chem. Bull.*, 2014, **63**, 2092.
- (a) P. Y. S. Lam, J. J. Adams, C. G. Clark, W. J. Calhoun, J. M. Luetzgen, R. M. Knabb and R. R. Wexler, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 1795; (b) M. L. McIntosh, M. R. Naffziger, B. O. Ashburn, L. N. Zakharov and R. G. Carter, *Org. Biomol. Chem.*, 2012, **10**, 9204; (c) B. A. Chalyk, I. Y. Kandaurova, K. V. Hrebeniuk, O. V. Manoilenko, I. B. Kulik, R. T. Iminov, V. Kubyshev, A. V. Tverdokhlebov, O. K. Ablialimov and P. K. Mykhailiuk, *RSC Adv.*, 2016, **6**, 25713; (d) M. A. Weidner-Wells, H. M. Werblood, R. Goldschmidt, K. Bush, B. D. Foleno, J. J. Hilliard, J. Melton, E. Wira and M. J. Macielag, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 3069.



- 15 (a) P. Conti, A. Pinto, L. Tamborini, P. Dunkel, V. Gambaro, G. L. Visconti and C. De Micheli, *Synthesis*, 2009, 591;
(b) E. Coutouli-Argyropoulou, P. Lianis, M. Mitakou, A. Giannoulisa and J. Nowak, *Tetrahedron*, 2006, **62**, 1494.
- 16 See section S1.2 in the ESI† for a detailed description of the experiments shown in Table 3.
- 17 O. V. Demina, A. A. Khodonov, E. I. Sinauridze, V. I. Shvets and S. D. Varfolomeeva, *Russ. Chem. Bull.*, 2014, **63**, 2092.

