EurJOC

European Journal of Organic Chemistry

Chemistry Europe

European Chemical Societies Publishing

Accepted Article

Title: The use of Potassium/Sodium Nitrite as a Nitrosating Agent in the Electrooxidative N-nitrosation of Secondary Amines

Authors: ying wang, shiqi You, Mengyao Ruan, Feiyi Wang, Chao Ma, cuifen Lu, Guichun Yang, zuxing Chen, and Meng Gao

To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.202100363

Link to VoR: https://doi.org/10.1002/ejoc.202100363

WILEY-VCH

WILEY-VCH

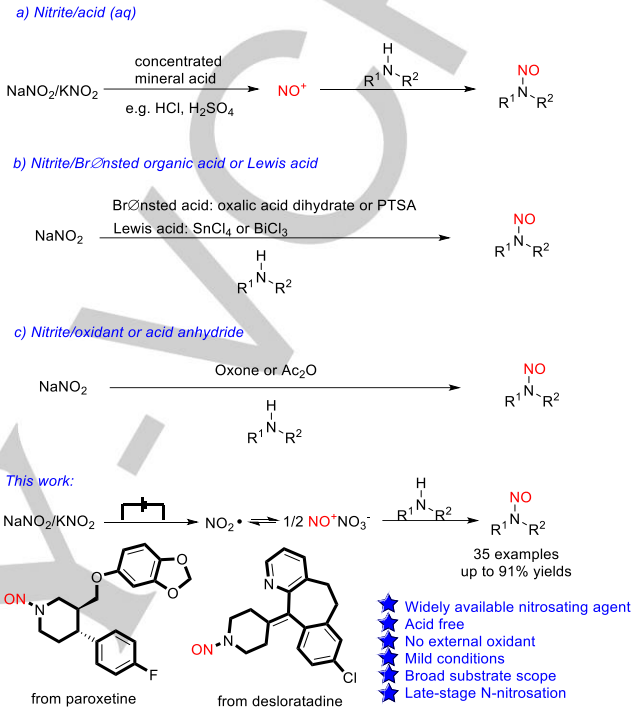
COMMUNICATION

The use of Potassium/Sodium Nitrite as a Nitrosating Agent in the Electrooxidative N-nitrosation of Secondary Amines

Ying Wang [a], Shiqi You [a], Mengyao Ruan [a], Feiyi Wang [a], Chao Ma [a], Cuifen Lu [a], Guichun Yang*[a], Zuxing Chen [a], Meng Gao*[a]

Abstract: We report herein on the electrochemical N-nitrosation of secondary amines using widely available sodium/potassium nitrite as a nitrosating agent. This approach not only eliminates the need for using a combination of sodium/potassium and a strong acid but also has good functional group tolerance. The reaction is compatible with the late-stage modification of pharmaceutical compounds and could be conducted in gram scale with a high reaction efficiency. Preliminary mechanistic studies indicate that the N-nitrosation occurs via the anodic oxidation of KNO_2 into an NO_2 radical which is then transformed into an NO^+ cation.

N-nitrosamine structures are a central core in a wide variety of naturally occurring and man-made compounds, which exhibit valuable biological and pharmaceutical properties.[1] For example, owing to their unique carcinogenic and mutagenic properties, N-nitrosamine derivatives have been used in the treatment of a variety of diseases including cancer, cardiovascular diseases and central nervous disorders,.[2] Apart from the wide biological importance of N-nitrosamines, they have also found broad use in both organic synthesis and in the field of material science.[3] N-nitrosamines are traditionally prepared by the polar addition of secondary amines and an in situ generated electrophilic NO+ cation under strongly acidic conditions.[4] The reaction of secondary amines and nitrous acid which are in situ generated from nitrite (e.g. $NaNO_2$, KNO_2) and a concentrated mineral acid (e.g. HCl, H_2SO_4) are currently the fundamental process for the production of N-nitrosamines on both laboratory and industrial scales (Scheme 1a).[5] This is because sodium/potassium nitrite are the most readily available nitrosating reagents. However, this strategy suffers from some innate issues including poor regioselectivity and imperfect functional group tolerance as well as the need for harsh conditions. Recent methodologies for the formation of N-nitroso compounds from mainly secondary amines have focused on the utilization of the classic nitrite reagent in combination with either an organic acid,[5d, 6] a Lewis acid,[5c, 7] an acid anhydride[8] or an oxidant,[9] in typical organic solvents (Scheme 1b and 1c). In addition, several other nitrosating agents were also developed which have significantly simplified the N-nitrosation process. These includealkyl nitrites,[10] nitrogen oxides,[11] Fremy's salt,[12] nitrosonium tetrafluoroborate,[13] nitroalkanes.[14] However, these methods all have some shortcomings, since they often required external oxidants or excess acid. Most of these agents and additives are not environmentally friendly and can be hazardous to handle and difficult to store. General protocols for the N-nitrosation of broad classes of secondary amines using these methods continue to be limited. In this context, the development of a straightforward, acid free and convenient route for activating the widely commercially available sodium/potassium nitrite for use in a N-nitrosation process would be highly attractive. It would not only eliminate the need for using a combination of sodium nitrite and a strong acid but would also address the above described limitations and provide a complementary application in organic synthesis, especially in late-stage N-nitrosation (Scheme 1).



Scheme 1. Electrochemical N-nitrosation using sodium/potassium nitrite as nitrosating agents

Organic electrosynthesis is now recognized as an efficient and environmentally benign synthetic strategy and has attracted significant interest.[15] Electrosynthesis could be used to achieve electron transfer between the electrodes and substrates or catalysts, thus avoiding the use of excess exogenous oxidants and would eliminate the generation of waste products. Very recently, Lu reported on an electrochemical N-nitrosation/N-nitration of secondary amines through a biradical coupling strategy.[16] The method employed a nitroso radical as the nitrosating agent which was generated in situ from the well-known thermal decomposition of iron(III) nitrate nonahydrate, $Fe(NO_3)_3{\cdot}9H_2O$. In the light of our continuous interest in organic

[a] Y. Wang, S. You, M. Ruan, F. Wang, C. Ma, C. Lu, Prof. G. Yang, Z. Chen, Prof. Dr. M. Gao
Ministry-of-Education Key Laboratory for the Synthesis and Application of Organic Functional Molecule & School of Chemistry and Chemical Engineering, Hubei University, Wuhan 430062, China.
E-mail: yangguichun@hubu.edu.cn; drmenggao@163.com

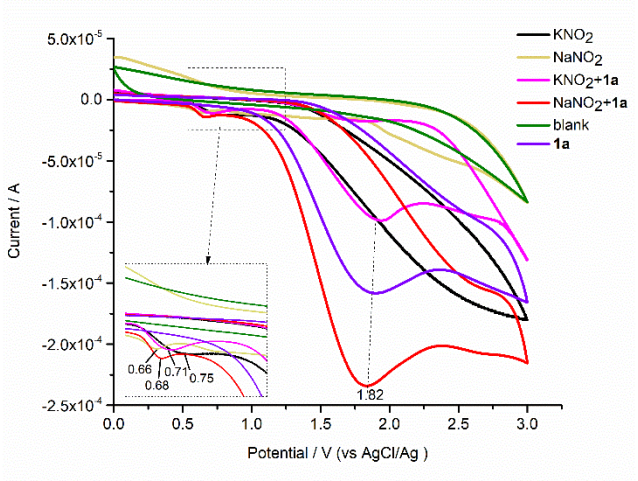
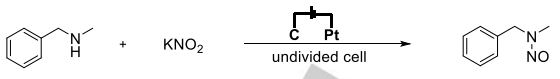


Figure 1 Cyclic voltammograms studies

electrosynthesis and N-H functionalization, we envisioned that N-nitrosation might be generally achieved by the direct activation of sodium/potassium nitrite through electroche mical strategies. To commence our study, we investigated the redox properties of sodium/potassium nitrite in cyclic voltammetry (Figure 1). The cyclic voltammograms showed irreversible oxidation waves for both sodium nitrite and potassium nitrite. These results indicate that they could be oxidized at the anode with the generation of a nitrogen dioxide radical. It was reported that nitrogen dioxide radicals could be transformed into an NO^+ cation through equilibrium which could then further react with secondary amines, thus leading to the formation of N-nitrosamines.[17] To confirm this hypothesis, N-methyl-1-phenylmethanamine was then added to capture the generated NO^+ cation. To our delight, the N-nitrosation product was indeed obtained. It is noteworthy that N-methyl-1-phenylmethanamine was oxidized at a much higher potential (1.82V) than both sodium nitrite (0.66 V) and potassium nitrite (0.75 V) which exclude the possibility that a biradical coupling pathway was involved in the process. This interesting transformation to N-nitrosamines encouraged us to further examine the feasibility of this efficient N-nitrosation.

Our investigation commenced be examining N-methyl-1-phenylmethanamine (**1a**) and KNO_2 (**2a**) as starting materials with DCM as the solvent. As shown in Table 1, by employing a two-electrode system with a carbon rod as the anode, a platinum plate as the cathode, and ^{n}Bu$_4$NBF$_4$ as the electrolyte, the desired N-nitrosation **3a** was produced in 89% yield with a constant, 5 mA current in an undivided cell (Table 1, entry 1). The use of $NaNO_2$ resulted in a reaction that was similar to that for KNO_2, albeit in lower yield (Table 1, entry 2). The use of a constant-current was crucial for the reaction and its omission resulted in no reaction (Table 1, entry 3) and the use of 5 mA proved to be the best option (Table 1, entries 3-5). Replacement of DCM by DCE or MeCN led to diminished yields (Table 1, entry 6 and 7). When EtOH was used, only a trace amount of the product was obtained (Table 1, entry 8). Regarding the choice of supporting electrolyte, both ^{n}Bu$_4$NClO$_4$ and ^{n}Bu$_4$NI were less effective than ^{n}Bu$_4$NBF$_4$ (Table 1, entry 9 and 10), and KI was found to be completely ineffective (Table 1, entry 11). It was noted that the product **3a** was obtained in only an 11% yield when a platinum plate cathode was used instead of a carbon rod cathode (Table 1, entry 12).

Table 1. Optimization of the reaction conditions [a]



Entry	Variation from the standard conditions	Yield[b]
1	none	89
2	$NaNO_2$ instead of KNO_2	60
3	0 mA	0
4	10 mA	70
5	2 mA	13
6	DCE instead of DCM	66
7	MeCN instead of DCM	9
8	EtOH instead of DCM	trace
9	^{n}Bu$_4$NClO$_4$ instead of ^{n}Bu$_4$NBF$_4$	81
10	^{n}Bu$_4$NI instead of ^{n}Bu$_4$NBF$_4$	30
11	KI instead of ^{n}Bu$_4$NBF$_4$	trace
12	graphite rod cathode instead of platinum plate	11

a) Reaction conditions: **1a** (0.5 mmol), **2a** (2.5 mmol), ^{n}Bu$_4$NBF$_4$ (0.3 mmol) in CH_2Cl_2 (7 mL), carbon rod as the anode and platinum plate as the cathode, undivided cell, constant current = 5 mA, r.t., 4 h; [b] isolated yields.

With the optimal conditions in hand, we next examined the scope of this electrochemical nitrosation reaction. As shown in scheme 2, various secondary amines were compatible under this reaction conditions and the corresponding products were produced in good yields. Both electron-donating and electron-withdrawing groups at the C2, C3, C4 and C5 positions of N-methyl-1-aryl substituted benzylamines were well-tolerated, giving the corresponding products in moderate to good yields ranging from 55% to 89% (**3a**-**3h**). N-allyl, ethyl, benzyl and tert-butyl substituted benzyl-amines also worked well in this transformation (**3i**-**3l**). Moreover, N-methyl-1-(pyridin-3-yl)methanamine and N-methyl-1-(thiophen-2-yl)methanamine were also found to be suitable reaction partners (**3m**-**3n**). Dibenzylamine and dicy-clohexylamine could also be readily converted into the corresponding products. Nitrosation reactions of cyclic amines were examined next. A series of cyclic secondary amines with different ring sizes provided moderate to good yields of the desired nitrosation products (**3q**-**3ac**). Moreover, A variety of functional groups on the cyclic secondary amines, such as mesyl (**3x**), phenyl (**3y**), and pyridinyl (**3aa**) groups were feasible. In order to test the compatibility of commonly used acid-labile protecting groups (tert-butyloxycarbonyl, Boc), tert-butyl piperidin-4-ylcarbamate was subjected to the N-nitrosation reaction under the optimized conditions. It was found that the Boc protecting group and the amide N-H bond remained stable during the reaction and the desired products (**3v**) were obtained in excellent yield (Scheme 4). The structure of **3v** was unambiguously confirmed by an X-ray crystallo-graphic analysis. Unfortunately, the secondary aromatic amines and primary amines cannot obtain the corresponding products or only gave the products in trace yields, possibly due to the easily oxidized property of these substrates under electrochemical oxidation conditions.

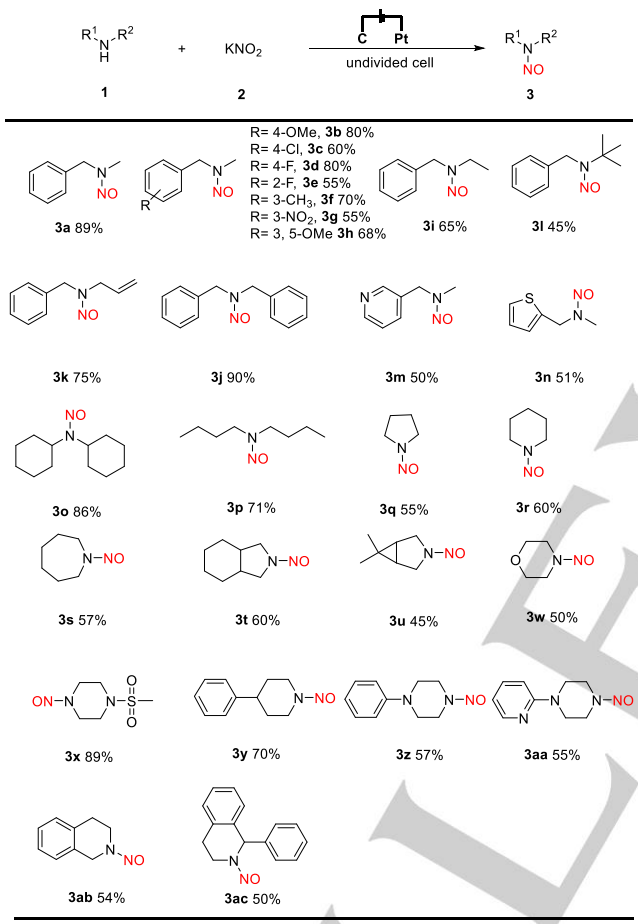
N-nitrosamines are an important class of biomolecules for which late-stage functionalization would be highly desirable. However, the traditional nitrosation protocols usually require strongly acidic conditions which limits their use in the synthesis of more complex molecules. We thus investigated the application of our N-nitrosation protocol in late-stage functionalization in this

10.1002/ejoc.202100363

COMMUNICATION

area (Scheme 3). To our delight, this method also proved to be applicable for the nitrosation of various important drug molecules and bioactive molecules, such as Troxipide, Praoxetine, Fluoxetine precursor, Cytisine, Desloratadine and Nortropine. The corresponding products were obtained in moderate to good yields under our electrochemical conditions (**3ad**-**3ai**). Meanwhile, in a gram-scale reaction using the established electrochemical strategy, good yields of the valuable N-Nitroso Desloratadine (CAS:1246819-22-6, 50 mg/1100 USD, from Trc) product **3ag** and N-Nitroso dicyclohexylamine product **3o** were offered, respectively (Scheme 4).

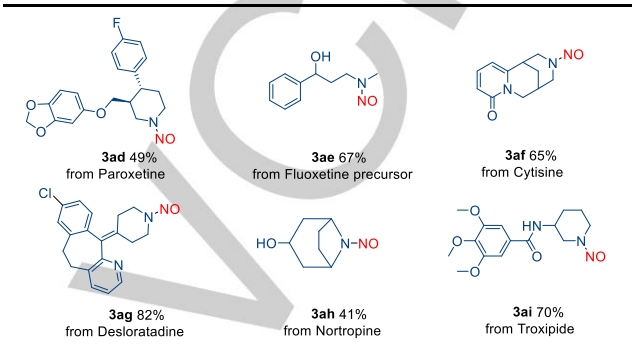
Scheme 2. Scope of Electrochemical N-nitrosation [a]



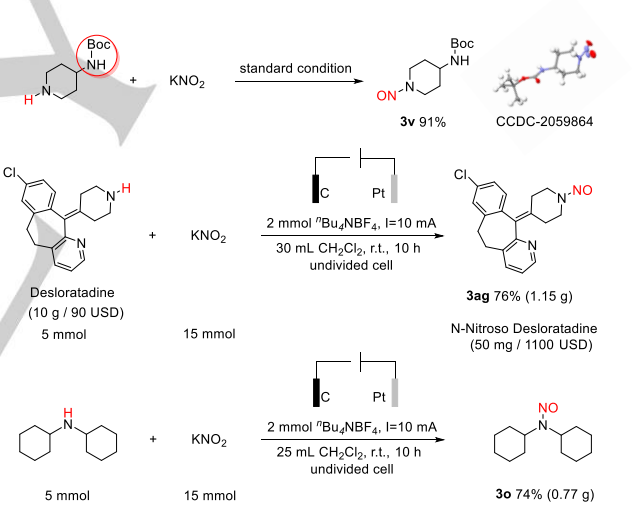
a) Reaction conditions: **1** (0.5 mmol), **2** (2.5 mmol), $^{n}Bu_4NBF_4$ (0.3 mmol) in CH_2Cl_2 (7 mL), carbon rod as the anode and platinum plate as the cathode, undivided cell, constant current = 5 mA, r.t., 4 h, isolated yields.

Mechanistic experiments were performed in an attempt to gain preliminary mechanistic information concerning this transformation. As shown in Figure 1 above, N-methyl-1-phenylmethanamine was oxidized at a much higher potential (1.82 V) than potassium nitrite (0.75V). In addition, the electrochemical behaviour of these compounds did not change substantially in the mixture (Scheme 2 purple line and red line). Thus, a controlled potential electrolysis was carried out. When the potential of the anode was maintained at 1.0 V where only potassium nitrite could be oxidized, the corresponding product was obtained in 47% yield. These results indicate that the oxidation of secondary amines on the anode was not essential for facilitating the reaction. When 1,1-diphenylethene (DPE) was added to the reaction between **1a** and **2a** under the standard conditions, only trace amount of N-nitrosamines was observed, and the DPE-NO_2 product was detected by GC−MS (Scheme 5). These results indicate that this reaction initially involves the generation of an NO_2 radical.

Scheme 3. Late-stage modification of complex and densely function-alized substrates [a]

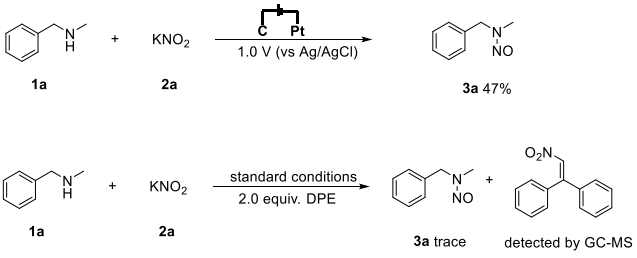


a) See Scheme 2 and also SI for detailed procedure.



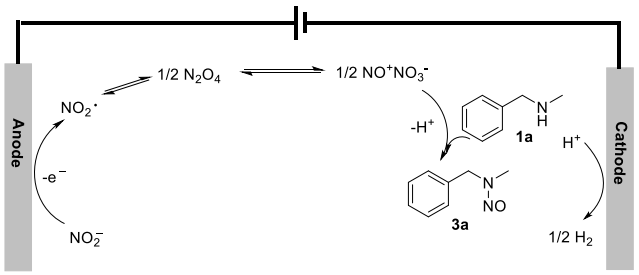
Scheme 4. Acid-labile substrate and reaction scale-up

Scheme 5. Mechanistic experiments.



Based on the above results and previous reports,[18] a plausible mechanism for this electrochemical N-nitrosation is illustrated in Scheme 6. First, NO_2^- is anodically oxidized to an

NO_2 radical, which undergoes rapid dimerization to generate N_2O_4. A NO^+ cation is then generated through equilibrium. Finally, a nucleophilic attack of the amine on NO^+ generates the desired product. At the same time, protons are reduced at the cathode with the formation of H_2.



Scheme 6. Plausible mechanism.

In summary, we report on the development of a straight-forward, acid free and convenient route to activate the widely commercially available potassium nitrite for use in N-nitrosation reactions. The reaction proceeds under exogenous-oxidant-free and acid-free electrochemical oxidation conditions, and a diverse collection of valuable N-nitrosation products were obtained in moderate to high yields. Notably, this electrochemical approach maintains excellent functional group tolerance and can be extended as a strategy for use in pharmaceutical research. Further detailed mechanistic studies regarding this transformation are currently under way in our laboratory.

Experimental Section

General procedure for electrochemical N-nitrosation of secondary amines: In an oven-dried undivided three-necked flask (25 mL) equipped with a stir bar, secondary amines **1** (0.50 mmol), KNO_2 **2** (2.5 mmol), CH_2Cl_2 (7 mL) with $^nBu_4NBF_4$ (0.30 mmol) as an electrolyte were combined and added. The flask was equipped with platinum electrodes (1.5 cm×1.5 cm×0.3 mm) as cathode, carbon rod (Φ 6 mm, about 10 mm immersion depth in solution) as the anode. The reaction mixture was stirred and electrolyzed at a constant current of 5 mA under room temperature for 4 h. After completion of the reaction, as indicated by TLC and GC-MS, the pure product was obtained by flash column chromatography on silica gel (petroleum ether : ethyl acetate = 50 : 1).

Acknowledgements

This work was supported by the National Natural Science Foundation of China (No. 21702081).

Keywords: Electrochemical synthesis • N-nitrosation • Acid free • Potassium Nitrite

[1] D. L. H. Williams, *Nitrosation Reactions and the Chemistry of Nitric Oxide*, Elsevier, Amsterdam, **2004**.

[2] a) P. Wang, T. Cai, N. Taniguchi, *Nitric Oxide Donors: For Pharmaceutical and Biological Applications*, **2005**, 1-390; b) P. G. Wang, M. Xian, X. Tang, X. Wu, Z. Wen, T. Cai, A. J. Janczuk, *Chem. Rev.*, **2002**, 102, 1091-1134.

[3] a) C. L. Bumgardner, K. S. McCallum, J. P. Freeman, *J. Am. Chem. Soc.*, **1961**, 83, 4417-4419; b) D. Seebach, D. Enders, Angew. Chem. Int. Ed., **1975**, 14, 15-32; c) T. Olszewska, M. J. Milewska, M. Gdaniec, H. Małuszyńska, T. Połoński, *J. Org. Chem*., **2001**, 66, 501-506.

[4] R. López-Rodríguez, J. A. McManus, N. S. Murphy, M. A. Ott, M. J. Burns, *Org. Process Res. Dev*., **2020**, 24, 1558-1585.

[5] a) G. Neurath and M. Dünger, *Chem. Ber.*, **1964**, 97, 2713-2714; b) M. A. Zolfigol, A. Bamoniri, *Synlett,* **2002**, 2002, 1621-1624; c) B. Célariès, C. Párkányi, *Synthesis,* **2006**, 2006, 2371-2375; d) S. P. Borikar, V. Paul, *Synth. Commun.*, **2010**, 40, 654-660.

[6] M. A. Zolfigol, *Synth. Commun.,* **1999**, 29, 905-910.

[7] A. C. Chaskar, B. P. Langi, A. Deorukhkar, H. Deokar, *Synth. Commun*., **2009**, 39, 604-612.

[8] J.-Y. Hou, Y.-L. Wang, J.-Y. Wang, *J. Chem. Res.*, **2003**, 2003, 626-627.

[9] P. Gaur and S. Banerjee, *Synth. Commun.*, **2019**, 49, 2270-2279.

[10] a) G. Verardo, A. G. Giumanini, P. Strazzolini, *Tetrahedron,* **1990**, 46, 4303-4332; b) D. Roche, C. Lardy, L. Tournier, M. Prunier, E. Valeur, *Tetrahedron Lett.*, **2010**, 51, 2277-2280; c) P. Chaudhary, S. Gupta, N. Muniyappan, S. Sabiah, J. Kandasamy, *Green Chem.*, **2016**, 18, 2323-2330; d) X. Guo, C. Lv, Q. Mahmood, L. Zhou, G. Xu, Q. Wang, *Org. Chem. Front.*, **2019**, 6, 3401-3407; e) X. Jia, P. Li, Y. Shao, Y. Yuan, H. Ji, W. Hou, X. Liu, X. Zhang, *Green Chem.*, **2017**, 19, 5568-5574; f) S. L. Yedage, B. M. Bhanage, *J. Org. Chem.*, **2017**, 82, 5769-5781; g) Y. He, Z. Zheng, Y. Liu, J. Qiao, X. Zhang, X. Fan, *Org. Lett.*, **2019**, 21, 1676-1680.

[11] a) E. H. White, *J. Am. Chem. Soc.*, **1955**, 77, 6008-6010; b) S. Goldstein, G. Czapski, *J. Am. Chem. Soc*., **1996**, 118, 3419-3425; c) N. S. Nudelman, A. E. Bonatti, *Synlett*, **2000**, 2000, 1825-1827; d) N. Iranpoor, H. Firouzabadi, A. R. Pourali, *Synth. Commun*., **2005**, 35, 1517-1526; e) E. H. White, W. R. Feldman, *J. Am. Chem. Soc.*, **1957**, 79, 5832-5833.

[12] L. Castedo, R. Riguera, M. P. Vázquez, *J. Chem. Soc., Chem. Commun.*, **1983**, 301-302.

[13] M. A. Zolfigol, M. H. Zebarjadian, G. Chehardoli, H. Keypour, S. Salehzadeh, M. Shamsipur, *J. Org. Chem.*, **2001**, 66, 3619-3620.

[14] a) A. S. Demir, A. S. Mahasneh, H. Aksoy, Z. Gercek, *Synth. Commun.*, **1992**, 22, 2607-2611; b) J. Zhang, J. Jiang, Y. Li and X. Wan, *J. Org. Chem.*, **2013**, 78, 11366-11372; c) N. Sakai, M. Sasaki, Y. Ogiwara, *Chem. Commun.*, **2015**, 51, 11638-11641; d) S. Azeez, P. Chaudhary, P. Sureshbabu, S. Sabiah, J. Kandasamy, *Asian J. Org. Chem.,* **2018**, 7, 2113-2119.

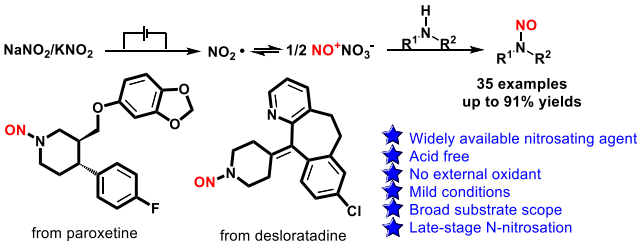
[15] For selected reviews, see: a) Y. Jiang, K. Xu, C. Zeng, *Chem. Rev.*, **2018**, 118, 4485-4540; b) M. Yan, Y. Kawamata and P. S. Baran, *Chem. Rev.*, **2017**, 117, 13230-13319; c) S. Möhle, M. Zirbes, E. Rodrigo, T. Gieshoff, A. Wiebe, S. R. Waldvogel, *Angew. Chem. Int. Ed.*, 2018, 57, 6018-6041; d) P. Gandeepan, L. H. Finger, T. H. Meyer, L. Ackermann, *Chem. Soc. Rev.,* **2020**, 49, 4254-4272; e) M. D. Kärkäs, *Chem. Soc. Rev.,* **2018**, 47, 5786-5865; f) S. Tang, Y. Liu, A. Lei, *Chem*, 2018, 4, 27-45; g) C. Ma, P. Fang, T.-S. Mei, *ACS Catal*., **2018**, 8, 7179-7189; h) J. C. Siu, N. Fu, S. Lin, *Acc. Chem. Res*., **2020**, 53, 547-560; i) P. Xiong, H.-C. Xu, *Acc. Chem. Res.*, **2019**, 52, 3339-3350.

[16] J.-P. Zhao, L.-j. Ding, P.-C. Wang, Y. Liu, M.-J. Huang, X.-L. Zhou, M. Lu, *Adv. Synth. Catal.*, **2020**, 362, 5036-5043.

[17] a) B. Su, L. Li, Y. Hu, Y. Liu, Q. Wang, *Adv. Synth. Catal.*, **2012**, 354, 383-387; b) G. V. Zyryanov, D. M. Rudkevich, *Org. Lett.*, **2003**, 5, 1253-1256; c) E. Bosch, J. K. Kochi, *J. Org. Chem*., 1994, 59, 3314-3325; d) M. A. Zolfigol, M. H. Zebarjadian, I. Mohammadpoor-Baltork, M. Shamsipur, *Synth. Commun.*, **2002**, 32, 2803-2808.

[18] a) T. Broder, D. Silvester, L. Aldous, C. Hardacre, R. Compton, *J. Phys. Chem. B*, **2007**, 111, 7778-7785; b) V. Bryantsev, J. Uddin, V. Giordani, W. Walker, G. Chase, D. Addison, *J. Am. Chem. Soc.*, **2014**, 136, 3087-3096.

Electrochemical synthesis



An efficient and environmentally electrooxidative N-nitrosation of secondary amines using potassium/sodium nitrite as nitrosating agents has been developed. This stragety break through the innate combination of sodium nitrite and a strong acid. The reaction is compatible with the late-stage modification of pharmaceutical compounds and could be conducted in gram scale with high reaction efficiency.