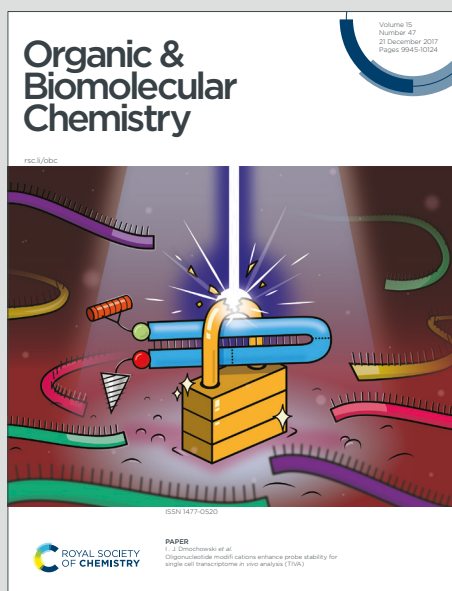


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ARTICLE

Metal free decarboxylative aminoxylation of carboxylic acids using a biphasic solvent system

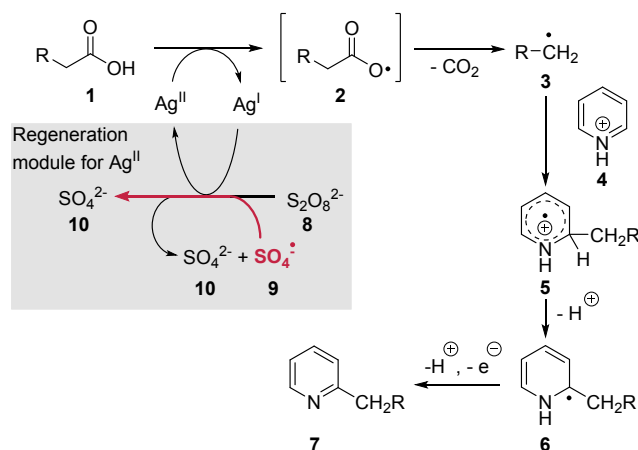
Göran Schulz,^a and Andreas Kirschning*^aReceived 00th January 20xx,
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Abstract: The smooth oxidative radical decarboxylation of carboxylic acids with TEMPO and other derivatives as radical scavengers is reported. The key to success was the use of a two-phase solvent system to avoid otherwise predominant side reactions such as the oxidation of TEMPO by persulfate and enabled the selective formation of synthetically useful alkoxyamines. The method does not require transition metals and was successfully used in a new synthetic approach for the antidepressant indatraline.

Introduction

The Minisci reaction is an oxidative radical decarboxylation reaction of carboxylic acids **1** first reported in the early 1970s (Scheme 1).¹ Mechanistically, the reaction is initiated by the oxidation of a silver(I) catalyst using potassium- or ammonium persulfate **8** as oxidant. In the presence of an Ag(I) salt persulfate dissociates to give two sulfate radicals **9** from where an electron is transferred onto Ag(I). Sulfate **10** is formed as a by-product. This process can be repeated with the second radical **9**. The active silver(II) species is next able to abstract the hydrogen atom from the carboxyl group in **1**.



Scheme 1: Proposed mechanism of the classical Minisci protocol for generation of alkyl radicals from alkyl carboxylic acids using silver (II).²

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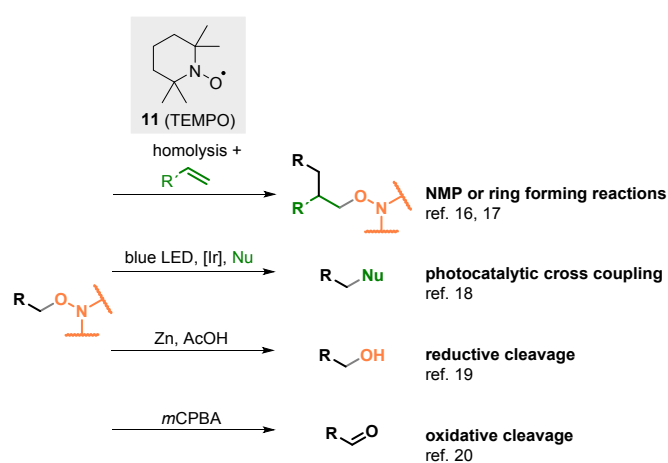
† Footnotes relating to the title and/or authors should appear here.
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

The resulting carboxyl radical **2** releases CO₂ to yield alkyl radical **3**, which adds to pyridinium cation **4**. The resulting radical cation **5** then rearomatizes via radical **6** after deprotonation and oxidation to form the alkylated pyridine **7** (Scheme 1). Thereby, silver(II) acts as oxidant being reduced to silver(I). Alternatively, it was reported that the oxidation of radical **6** can also be promoted by the sulfate radical **9** to furnish sulfate **10**.² Over the past decade, this decarboxylative alkyl radical forming process has been utilised in numerous C-C³ and C-S⁴ coupling reactions, ring closing cascades,⁵ radical substitutions⁶ and azidations.⁷

Despite extensive research in this field, controlled and selective decarboxylations of this type still have some disadvantages. Often up to stoichiometric amounts of the expensive silver(I) salts are required.^{3,4,5a} In selected rare cases it has been shown that the addition of a base can eliminate the need for transition metal catalysts.^{8,9} In fact, the sulfate radical **9** with a redox potential of 2.5-3.1 V is a strong single electron oxidant and can therefore form carboxyl radicals **2** from the carboxylates generated *in situ*.¹⁰ Particularly with the metal-free variants, but also with the silver-catalysed methods, the low selectivity is revealed by the fact that carboxylic acid **1** must be used in excess.^{8,9,11} In addition, the strongly oxidising conditions significantly limit the substrate and reagent range. This obstacle becomes clear, for example, when using a very common method for investigating radical mechanisms. By adding aminoxy radicals such as 2,2,6,6-tetramethylpiperidin-1-yloxy (TEMPO, **11**) to the reaction mixture, highly reactive radical intermediates can be captured and identified as alkoxyamines.^{12,13} In the Minisci reaction, this method was used to determine mechanistic details and the resulting alkoxyamines were usually confirmed by mass spectrometry.^{8,14} One reason why this reaction has not been used preparatively so far is probably that TEMPO can be oxidised by peroxodisulfate salts.¹⁵

But alkoxyamines are an important group of reagents and functional groups widely used in organic chemistry (Scheme 2).

They serve as initiators for the nitroxide-mediated polymerisation (NMP), a radical polymerisation induced by homolytic cleavage of the C-ON bond, in most cases under thermolytic conditions. The highly reactive alkyl radical and the persistent aminoxyl radical react with alkenes by a migratory insertion into the double bond.¹⁶ This reaction type has also been successfully employed in synthetic organic chemistry for ring-closing reactions.¹⁷ In 2016, Knowles et al. reported on the mesolytic cleavage of alkoxyamines by photoredox catalysis. The cross-coupling of the resulting carbocations with various nucleophiles led to the formation of new C-C, C-N or C-O bonds.¹⁸ Beyond these applications, alkoxyamines can easily be converted into alcohols¹⁹ or carbonyl compounds.²⁰ Existing methods to form alkoxyamines start from haloalkanes,²¹ boronates,²² boranes,²³ aldehydes^{12,13,24} or redox active esters²⁵.



Scheme 2: Selected applications of alkoxyamines in organic chemistry.

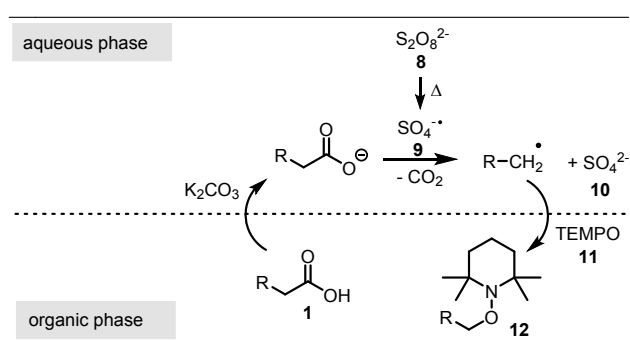
In view of these diverse considerations, we initiated a program to develop a method for the formation of alkoxyamines from carboxylic acids by metal-free radical decarboxylation.

Results and Discussions

Optimisation of reaction conditions

In literature, single-phase solvent systems have been used for metal-free as well as the common silver-catalysed decarboxylative transformations using peroxodisulfate salts. Usually water is combined with a polar solvent such as acetonitrile,^{8,19} conditions that are not suitable if aminoxyl radicals like TEMPO **11** are employed due to the presence of peroxodisulfate salts.²⁰ We assumed that this side reaction can be suppressed by using a two-phase system to keep the oxidant in a separate compartment from the aminoxyl radical. Mechanistically, the carboxylic acid **1** is first deprotonated at the phase boundary using potassium carbonate as base. Since the carboxylate and the peroxodisulfate salt **8** are water-soluble, the oxidative decarboxylation should take place in the aqueous phase. As a result a less polar alkyl radical is formed, which in turn is trapped by TEMPO (**11**) in the organic phase to yield the alkoxyamine **12**.

Following this hypothesis, we optimised the conditions of decarboxylative aminoxylation using biphenylacetic acid (**1a**) as model acid. A mixture of **1a**, TEMPO **11** (2.0 eq.), potassium persulfate (3.0 eq.) and K₂CO₃ (1.5 eq.) was stirred for 20 h at rt in 1,2-dichloroethane and water (1:1). We started with an excess of TEMPO **11** because in single-phase solvent systems the yields were greatly reduced due to the oxidation of TEMPO by persulfate. After extraction of the reaction mixture with EtOAc, alkoxyamine **12a** was collected in 11% yield. However, we also observed the formation of benzophenone (**13**) (Table 1, entry 1). This oxidative transformation upon treatment of phenylacetic acid derivatives with K₂S₂O₈ in water has already been reported in 2017 by Bhat et al. They proposed that the benzyl radical could be oxidised to a cation by the sulfate radical. After the nucleophilic addition of water, a second oxidation takes place, which leads to the observed carbonyl product.²⁶



Scheme 3: Proposed phase-transfer concept for the decarboxylative aminoxylation reported here.

Table 1 Optimisation of transition-metal free decarboxylative aminoxylation of carboxylic acid **13a** (DCE= 1,2-dichloroethane).

entry	K ₂ S ₂ O ₈ [eq.]	solvent mix. (v:v)	T [°C]	12a ^a [%]	13 ^a [%]
1	3.0	DCE/H ₂ O (1:1)	25	11	39
2	3.0	DCE/H ₂ O (2:1)	80	28	30
3	1.0	DCE/H ₂ O (2:1)	80	49	13
4	1.0	DCE/H ₂ O (3:1)	80	60 (59)	11
5 ^b	1.0	DCE/H ₂ O (3:1)	80	(56)	n.d.
6 ^c	1.0	DCE/H ₂ O (3:1)	80	46	22
7 ^d	1.0	DCE/H ₂ O (3:1)	80	27	28
8	1.0	MeCN/H ₂ O (3:1)	80	2	36
9	1.0	DMF/H ₂ O (3:1)	80	3	2
10	(NH ₄) ₂ S ₂ O ₈ (1.0 eq.), AgNO ₃ (2.5 mol%), CH ₂ Cl ₂ /H ₂ O (1:1), rt., 6 h (ref. 27)			< 1	18

^a ¹H NMR-yields using naphthalene as an internal standard; yields in brackets are isolated yields; ; ^b 1.0 eq. of TEMPO; ^c Na₂S₂O₈ was used instead of K₂S₂O₈; ^d (NH₄)₂S₂O₈ was used instead of K₂S₂O₈; n.d. = not detected.

Following this proposal, we assumed that changing the ratio of DCE and water in favour to the former should reduce by-product formation. Additionally, we raised the reaction

temperature to 80 °C to accelerate the decarboxylation step. With these changes of conditions the yield for alkoxyamine **12a** could be raised to 28% (entry 2) with benzophenone (**13**) still being formed as the main product. As a result, the amount of oxidising agent was reduced to one equivalent. The yield for **12a** was now at 49% (entry 3). In contrast, both a higher amount of base and its absence led to a decrease in yield.

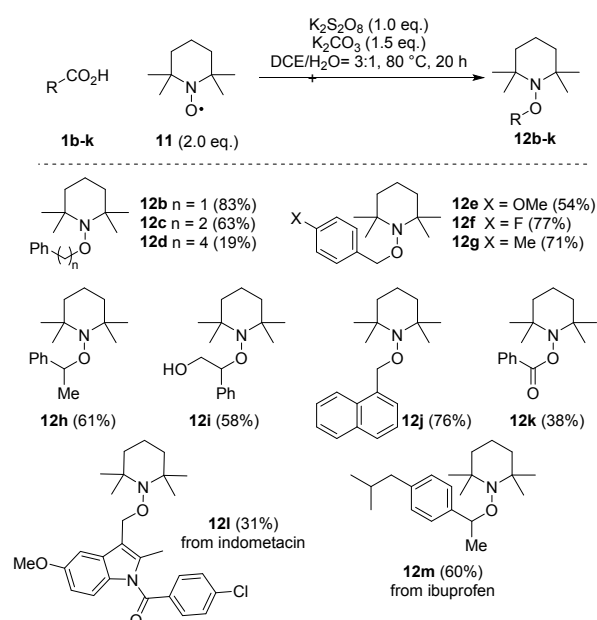
A dichloroethane-water ratio of 3:1 further improved the yield in favour of **12a** to 60% (59% isolated yield) (entry 4). The reduction of the TEMPO amount from two to one equivalent resulted in comparable yield (entry 5). This indicates that only a very small amount of TEMPO is oxidized under the reaction conditions. Principally, the use of one equiv. of TEMPO is also feasible. However, if more polar, water-soluble aminoxyl radicals are used, an excess of the radical would likely be beneficial. The counter ion of the oxidising agent exerts a non-negligible influence on the transformation, as shown by the lower yields when using sodium or ammonium persulfate (entries 6 and 7). Finally, the reaction was repeated using acetonitrile or DMF as co-solvents (entries 8 and 9), with a dramatic decrease in yield, confirming the need for a two-phase system for the reasons given above.

In 2014, Xia et al. reported on the alkylation of purine nucleosides, whereby silver catalysis was also used in a Minisci-type reaction.²⁷ The authors investigated the mechanism of this transformation by adding TEMPO to the reaction mixture. According to their experimental data, the resulting alkoxyamine could be obtained in 87% yield from cyclohexanecarboxylic acid. We repeated the experiment under exactly the conditions described by Xia and colleagues. When cyclohexanecarboxylic acid was used, we observed a lower conversion rate, with only traces of the desired product being formed. For diphenylacetic acid (**1a**) the yield of **12a** was less than 1%, while benzophenone (**13**) formed as the main product (entry 10).

Substrate scope and limitations

With the present optimised conditions, we extended the usability of this reaction to further carboxylic acids (Scheme 4). If aromatic substituents are present, the positioning of this substituent relative to the carboxyl group has a major influence on the result. Arylacetic acid derivatives provide medium to high yields, precisely because it is assumed that an aryl-stabilised benzylic radical is formed intermediately. With an increasing number of carbon atoms between the carboxyl group and the aryl substituent, the yields decrease (**1b-d** → **12b-d**). Benzyl cation stabilising substituents like the 4-methoxy group, however, favour over-oxidation and formation of the acetophenone derivative, resulting in a reduced yield of 54% for alkoxyamine **12e**. The use of the toluene derivative **1g** reveals the chemoselectivity of this method, as the methyl substituent remained untouched. Other functional groups noteworthy alcohols (tropic acid **1i** → **12i**) are tolerated. However, we found that the presence of amino groups as in *N*-Boc-phenylglycine, *p*-aminophenylacetic acid and 3-amino-2-phenylpropionic acid resulted in complex mixtures, which in the range of $\delta = 10$ ppm in the ¹H-NMR spectrum showed signals indicating the presence

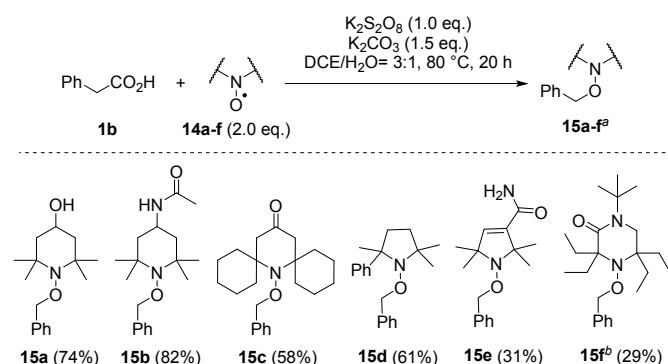
of aldehydes and/or imines or, in the case of the aniline derivative, polymeric materials. The decarboxylative aminooxylation presented here also allows easy access to alkoxyamine **12h**, an important initiator of the nitroxide-mediated polymerisation (NMP).²⁸ When using α -keto acid **1k**, a biologically significant reaction type is achieved, which provides the TEMPO ester **12k**. Such oxidative decarboxylations are widespread processes in nature. For example, the oxoglutarate dehydrogenase complex (OGDC), which is found in the citrate cycle, catalyses the oxidative decarboxylation of α -ketoglutarate to succinyl-CoA.²⁹ Finally, we also performed decarboxylations on two more complex acids, namely indometacin and ibuprofen, which provided the TEMPO derivatives **12l** and **12m** in moderate to good yields. When using acids that lack aryl components, such as cyclohexanecarboxylic acid, 1-adamantanecarboxylic acid and 2-methylpentanoic acid, the formation of the desired alkoxyamines was only detected in trace amounts. Instead, we observed mainly non-decarboxylating C-H activations in different positions within the alkyl backbone.



Scheme 4 Substrate scope of the radical decarboxylative aminooxylation.

This radical decarboxylation can be conducted with other TEMPO derivatives **14a-f** using phenylacetic acid **1b** as model substrate. In applications of alkoxyamines in nitroxide-mediated polymerisations and also in the cyclisation reactions in organic synthesis, the structure of the aminoxyl radicals used plays an important role.¹⁶

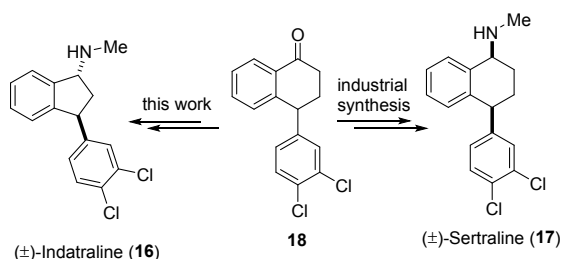
Both the dissociation and the recombination rate of the C-O bond, whose homolytic cleavage initiates the radical cross-coupling reaction cascade, depends strongly on the structure of the aminoxyl radical. This concerns the ring size, the steric size as well as the polarity of the persistent radical.³⁰



Scheme 5 Use of other aminoxy radicals **14a-f** in oxidative decarboxylations with phenylacetic acid (**1b**) (^a isolated yields, ^b **15f** turned out to be unstable at elevated temperatures).

Synthesis of (±)-Indatraline

Indatraline (Lu 19-005, **16**) is a non-selective inhibitor of the monoamine transporter. It is able to block the reuptake of dopamine, norepinephrine, and serotonin very similar to cocaine. In addition, indatraline is used to block the effects of methamphetamine and MDMA.³¹ Sertraline (**17**), a structurally closely related drug, is one of the best-selling antidepressants and, with over 38 million prescriptions in 2017, the 14th most prescribed drug in the United States.³² Here we show the application of our decarboxylative amination in a new synthetic approach to (±)-indatraline (**16**). The starting point is the advanced intermediate **18** from the industrial sertraline (**17**) synthesis (Scheme 6)

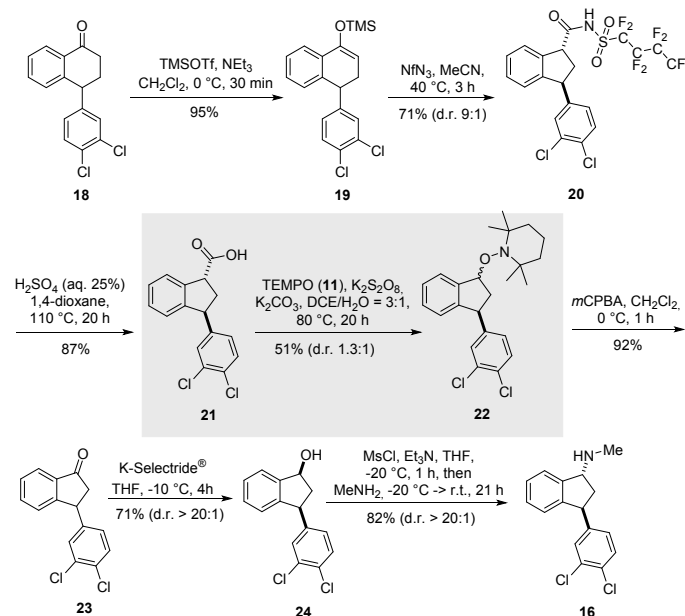


Scheme 6 Advanced intermediate **18** of the industrial sertraline (**17**) synthesis as a starting point for a new total synthesis of indatraline (**16**).

Our synthesis started with a Favorskii-type ring contraction using a slightly modified two-step protocol originally reported by the Herzon group (Scheme 7).³³ First, we treated tetralone **18** with trimethylsilyltrifluoromethanesulfonate and triethylamine to obtain TMS-enol ether **19** almost quantitatively. The subsequent click reaction with nonaflyl azide and the resulting nitrogen-releasing rearrangement led to amide **20** as *anti*-diastereomer d.r. (9:1) in 71% yield.

The saponification of amide **20** proved to be problematic, since methods for the hydrolysis of nonaflyl amides have not yet been reported. Alkaline conditions were unsuccessful, probably because of the strong electron-withdrawing effect of the nonaflyl group, which stabilises a negative charge on the nitrogen atom. However, under acidic conditions, using a mixture of aqueous sulfuric acid and 1,4-dioxane at 100 °C, carboxylic acid **21** was obtained in 87% yield. Next, the key step

of the synthesis, the protocol of oxidative decarboxylation presented here, was investigated, and fortunately we collected alkoxyamine **22** in 51% yield. The oxidation of alkoxyamine by *m*CPBA resulted in indenone **23** in 92% yield. The synthesis was then completed according to the established protocols of Davies³⁴ and Froimowitz.³⁵ This included diastereoselective reduction with K-Selectride®. The resulting *syn*-indenol **24** was finally converted into (±) indatraline (**16**) by mesylation and subsequent nucleophilic substitution with methylamine.



Scheme 7 A new total synthesis approach for (±)-indatraline (**16**) based on the decarboxylative amination of carboxylic acid **21**.

Conclusions

In summary, we reported on the first general method for the direct synthesis of alkoxyamines from carboxylic acids. By using a biphasic solvent system, we were able to suppress known side reactions and thus perform radical decarboxylation and subsequent capture of the alkyl radical with structurally different aminoxy radicals with high chemoselectivity. This allowed us to completely avoid the use of transition metal catalysts.³⁷

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Experimental Procedures

Procedure for the radical decarboxylative amination exemplified for phenylacetic acid (**1b**)

A vial charged with phenylacetic acid (**1b**) (27 mg, 200 μ mol, 1.00 equiv.), TEMPO (**11**) (64 mg, 400 μ mol, 2.0 equiv.), potassium carbonate (41 mg, 300 μ mol, 1.50 equiv.) and

potassium peroxodisulfate (54 mg, 200 μmol , 1.0 equiv.) was evacuated and purged with argon and 1,2-dichloroethane (1.50 mL) and water (0.50 mL) were added. The biphasic mixture was stirred at 80 $^{\circ}\text{C}$ under an argon atmosphere for 20 h. Then, the reaction mixture was diluted water (5.0 mL) and extracted with EtOAc (3x 10.0 mL). The combined organic phases were washed with brine (10.0 mL), dried over MgSO_4 , filtered and concentrated under reduced pressure. The product was purified by flash column chromatography (petroleum ether:EtOAc= 50:1). The alkoxyamine **12b** was collected as a pale-yellow oil (41 mg, 166 μmol , 83%). R_f = 0.50 (petroleum ether:EtOAc 50:1); $^1\text{H-NMR}$ (CDCl_3 , 600 MHz): δ [ppm] 7.38 - 7.28 (m, 5H, ArH), 4.83 (s, 2H, CH_2ON), 1.64 - 1.34 (m, 6H, $3\times\text{CH}_2$), 1.26 (s, 6H, $2\times\text{CH}_3$), 1.16 (s, 6H, $2\times\text{CH}_3$); $^{13}\text{C-NMR}$ (CDCl_3 , 150 MHz): δ [ppm] 138.5 (q, ArC), 128.4 (t, $2\times\text{ArC}$), 127.6 (t, $2\times\text{ArC}$), 127.4 (t, ArC), 78.9 (s, CH_2ON), 60.2 (q, $2\times\text{C}(\text{CH}_3)_2$), 39.9 (s, $2\times\text{CH}_2$), 33.2 (p, $2\times\text{CH}_3$), 20.4 (p, $2\times\text{CH}_3$), 17.3 (s, $\text{CH}_2(\text{CH}_2)_2$). The analytical data are consistent with those reported in the literature.³⁵

Notes and references

- 1 F. Minisci, R. Bernardi, F. Bertini, R. Galli, and M. Perchinummo, *Tetrahedron* 1971, **27**, 3575.
- 2 R. S. J. Proctor, and R. J. Phipps, *Angew. Chem. Int. Ed.* 2019, **58**, 13666.
- 3 W.-M. Zhao, X.-L. Chen, J.-W. Yuan, L.-B. Qu, L.-K. Duan, and Y.-F. Zhao, *Chem. Commun.* 2014, **50**, 2018.
- 4 P.-F. Wang, X.-Q. Wang, J.-J. Dai, Y.-S. Feng, and H.-J. Xu, *Org. Lett.* 2014, **16**, 4586.
- 5 a) K. Yan, D. Yang, W. Wei, F. Wang, Y. Shuai, and Q. Li, H. Wang, *J. Org. Chem.* 2015, **80**, 1550; b) S. Seo, M. Slater, M. F. Greaney, *Org. Lett.* 2012, **14**, 2650.
- 6 L. Cui, H. Chen, C. Liu, and C. Li, *Org. Lett.* 2016, **18**, 2188.
- 7 C. Liu, X. Wang, Z. Li, L. Cui, and C. Li, *J. Am. Chem. Soc.* 2015, **137**, 9820.
- 8 S. Lu, Y. Gong, and D. Zhou, *J. Org. Chem.* 2015, **80**, 9336.
- 9 J. K. Laha, K. V. Patel, K. S. S. Tummalapalli, and N. Dayal, *Chem. Commun.* 2016, **52**, 10245.
- 10 a) M. Brienza, and I. Katsoyiannis, *Sustainability* 2017, **9**, 1604; b) L. W. Matzek, and K. E. Carter, *Chemosphere* 2016, **151**, 178.
- 11 S. Mandal, T. Bera, G. Dubey, J. Saha, and J. K. Laha, *ACS Catal.* 2018, **8**, 5085.
- 12 A. Kipke, K.-U. Schöning, M. Yusubov, and A. Kirschning, *Eur. J. Org. Chem.* 2017, 6906.
- 13 K.-U. Schöning, W. Fischer, S. Hauck, A. Dichtl, and M. Kuepfert, *J. Org. Chem.* 2009, **74**, 1567.
- 14 a) L. Lv, S. Lu, Y. Chen, and Z. Li, *Org. Chem. Front.* 2017, **4**, 2147; b) Y. Li, M. Hu, and J.-H. Li, *ACS Catal.* 2017, **7**, 6757; c) G. Hong, J. Yuan, J. Fu, G. Pan, Z. Wang, L. Yang, Y. Xiao, P. Mao, and X. Zhang, *Org. Chem. Front.* 2019, **6**, 1173; d) J. Li, W.-J. Hao, P. Zhou, Y.-L. Zhu, S.-L. Wang, S.-J. Tu, and B. Jiang, *RSC Adv.* 2017, **7**, 9693.
- 15 P. Gao, J. Wang, Z. Bai, M.-J. Fan, D.-S. Yang, and Z.-H. Guan, *Org. Lett.* 2018, **20**, 3627.
- 16 L. Tebben, and A. Studer, *Angew. Chem. Int. Ed.* 2011, **50**, 5034.
- 17 a) A. Studer, *Angew. Chem. Int. Ed.* 2000, **39**, 1108; b) M. Šimek, K. Bártová, R. Pohl, I. Císařová, and U. Jahn, *Angew. Chem. Int. Ed.* 2020, **59**, 6160.
- 18 Q. Zhu, E. C. Gentry, and R. R. Knowles, *Angew. Chem. Int. Ed.* 2016, **55**, 9969.
- 19 A. R. Howell, and G. Pattenden, *J. Chem. Soc., Chem. Commun.* 1990, 103. DOI: 10.1039/DO0B01773F
- 20 T. Inokuchi, and H. Kawafuchi, *Tetrahedron* 2004, **51**, 11969.
- 21 a) R. Braslau, A. Tsimelzon, and J. Gewandter, *Org. Lett.* 2004, **6**, 2233; b) J.-L. Counturier, and O. Guerret, WO 2002012149, 2002; c) J.-L. Counturier, and O. Guerret, WO 2000061544, 2000; d) T. J. Connolly, M. V. Baldoví, N. Mohtat, and J. C. Scaiano, *Tetrahedron Lett.* 1996, **37**, 4919.
- 22 C. Cadot, P. I. Dalko, J. Cossy, C. Ollivier, R. Chuard, and P. Renaud, *J. Org. Chem.* 2002, **67**, 7193.
- 23 C. Ollivier, R. Chuard, and P. Renaud, *Synlett* 1999, 807.
- 24 K.-U. Schöning, W. Fischer, A.-I. Basbas, and A. Dichtl, WO 2008003602, 2008.
- 25 Zheng, Y. Wang, Y. Xu, Z. Chen, G. Chen, and S. H. Liang, *Org. Lett.* 2018, **20**, 4824.
- 26 T. B. Mete, T. M. Khopade, R. G. Bhat, *Tetrahedron Lett.* 2017, **58**, 2822.
- 27 R. Xia, M.-S. Xie, H.-Y. Niu, G.-R. Qu, and H.-M. Guo, *Org. Lett.* 2014, **16**, 444.
- 28 T. J. Connolly, M. V. Baldoví, N. Mohtat, and J. C. Scaiano, *Tetrahedron Lett.* 1996, **37**, 4919.
- 29 L. A. Moran, H. R. Horton, K. G. Scrimgeour, and M. D. Perry, *Principles of biochemistry*, Pearson Education, 2012, p. 394-402.
- 30 G. Audran, P. Brémond, and S. R. A. Marque, *Chem. Commun.* 2014, **50**, 7921.
- 31 R. B. Rothman, J. S. Partilla, M. H. Baumann, C. M. Dersch, F. I. Carroll, and K. C. Rice, *Synapse* 2000, **35**, 222.
- 32 ClinCalc DrugStats Database, "The Top 300 of 2020", <https://clincalc.com/DrugStats/Top300Drugs.aspx>, 2020.
- 33 M. J. Mitcheltree, Z. A. Konst, S. B. Herzon, *Tetrahedron* 2013, **69**, 5634.
- 34 H. M.L. Davies, and T. M. Gregg, *Tetrahedron Lett.* 2002, **43**, 4951.
- 35 M. Froimowitz, K. M. Wu, A. Moussa, R. M. Haidar, J. Jurayj, C. George, and E. L. Gardner, *J. Med. Chem.* 2000, **43**, 4981.
- 36 Y. Yasu, T. Koike, and M. Akita, *Adv. Synth. Catal.* 2012, **354**, 3414.
- 37 For a recent copper-mediated oxidative decarboxylation followed by alkylation of secondary amines see: D. Kong, P. J. Moon, O. Bsharat, and R. J. Lundgren, *Angew. Chem. Int. Ed.* 2020, **59**, 1313.

Graphical abstract

The oxidative radical decarboxylation of carboxylic acids with TEMPO as radical scavenger in a biphasic solvent system is reported which is successfully used in a new synthetic approach for the antidepressants Indatraline.

