How to cite: *Angew. Chem. Int. Ed.* **2023,** *62,* e202215916
International Edition: doi.org/10.1002/anie.202215916
German Edition: doi.org/10.1002/ange.202215916

N-Heterocycles

The Eschenmoser's Salt as a Formylation Agent for the Synthesis of Indolizinecarbaldehydes and Their Use for Colorimetric Nitrite Detection

*Teresa Antón-Cánovas and Francisco Alonso**

Dedicated to Professor Irina P. Beletskaya on the occasion of her 90th birthday

Abstract: C–H bond formylation is the most immediate way to incorporate the versatile formyl group into (hetero)aromatics. However, the type of reagents and severe conditions involved in the classical formylation methods often curtail their application, especially in the presence of other functional groups. Herein, we present the Eschenmoser's salt, a commercially available (dimethylamino)methylating chemical, as a useful reagent for the C–H formylation of indolizines and other compounds. The method is straightforward and mild, furnishing indolizinecarbaldehydes in modest-to-good yields with exclusive and remote regioselectivity. Furthermore, these compounds can be easily transformed into push-pull dyes and are highly selective in the colorimetric detection of nitrite, a substance extensively employed as preservative in the food industry, the concentration of which is crucial to control to prevent harmful effects in living organisms. The assay is simple, allowing the naked-eye detection of nitrite in solution or on a cotton swab for a wide range of concentrations.

Introduction

In recent years, late-stage and remote C–H functionalization have received a great deal of attention in drug discovery because they allow to access molecules of interest through new disconnections with high atom and step economy.[1] The formyl group is a very versatile functionality in synthetic organic chemistry,[2] as well as in the field of colorimetric and fluorimetric chemosensors.[3] Its incorporation into (hetero)aromatic compounds generally relies on classical formylation methods,[4] namely: the Vilsmeier–Haack,[5] Reimer-Tiemann,[6] Duff[7] and Gatterman[8] reactions, or the metalation-formylation with DMF. However, the harsh reagents and conditions involved in these methods often lead to low yields and poor selectivities, particularly, when sensitive functional groups are present. An unprecedented transition-metal catalyzed formylation of heteroarenes by C–H activation, lately reported by the group of Glorius, is praiseworthy.[9] Indolizines are privileged molecular platforms in synthetic heterocyclic chemistry[10] and in drug discovery, being present in relevant pharmacologically-active compounds (Figure 1, **I–X**),[11] and with manifold applications in materials science because of their prominent photophysical properties (Figure 1, **XI–XV**).[12] The differ-

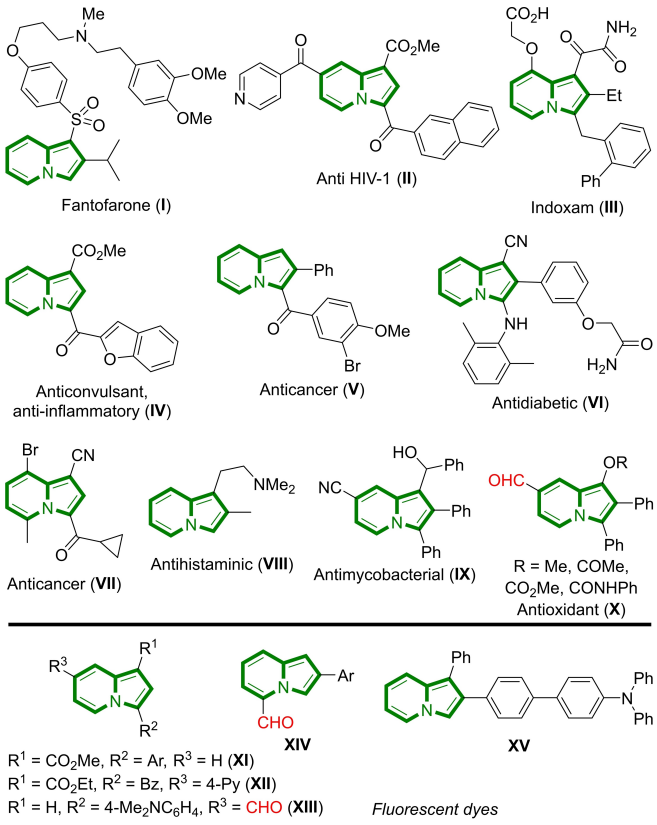


Figure 1. Pharmacological and photophysical properties of some indolizines.

[*] T. Antón-Cánovas, Prof. Dr. F. Alonso
Instituto de Síntesis Orgánica and Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Alicante
Apdo. 99, 03080 Alicante (Spain)
E-mail: falonso@ua.es

ently substituted indolizines depicted in Figure 1 give an idea on the varied activities exhibited by this type of heterocycles.[11] For instance, fantofarone (**I**) is a calcium-channel blocker used in the treatment of vasospasms;[13a] compound **II** was identified as a strong HIV-1 viron infectivity factor inhibitor;[13b] indoxam (**III**) is an effective inhibitor of secretary phospholipase A2 (s-PLA2),[13c] which related 2-(indolizin-1-yl)-2-oxoacetamides manifest comparable cytotoxicity to that of taxol;[13d] and indolizines **V** and **VII** have shown antiproliferative activity against human neuroblastoma (BE2-C)[13e] and liver carcinoma (Hep-G2) cells,[13f] respectively. It is worthy of note that the indolizine-7-carbaldehydes **X** are potent antioxidants, displaying intense inhibition of lipid peroxidation.[13g] The synthesis of indolizine-7-carbaldehydes typically requires the pre-installation of the formyl group in the starting materials or the transformation of a precursor functional group.[12e,13g,14] Therefore, on the basis of what aforesaid, it is timely to develop new late-stage C–H formylation methods of heterocycles that allow, among others, the synthesis of indolizine-carbaldehydes in a chemo- and regioselective manner.

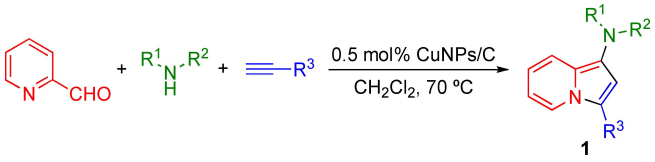
In a different context, nitrites can be found naturally in water and are widely used as food additives for preservation or color fixation purposes.[15] However, its accumulation in both physiological and environmental systems can have a detrimental effect on the health of mammals, invertebrates and aquatic organisms. Despite protecting food from microorganisms (e.g., *Clostridium botulinum*), nitrites can react with secondary and tertiary amines, under the acidic conditions in the stomach, to produce highly carcinogenic *N*-nitrosamines which, ultimately, might lead to esophageal, gastric or colorectal cancer.[16] The important need to control the levels of nitrite in the recent decades has triggered the development of multiple analytical methods, most of them based on chromatographic, spectroscopic and electrochemical detection.[17] Colorimetric detection methods, which can visually provide enough analytical information, are cost-effective and far more convenient because of their simplicity and easy applicability.[18] They usually rely on the acidic-medium induced diazotization of an amine indicator with the nitrite of the sample, followed by the coupling with a secondary species that gives an azo chromophore (Griess test).[19] Though widely deployed to quantify nitrite in food, this standard test has some disadvantages, such as the need to control the reaction to avoid diazonium-salt decomposition before coupling, narrow working concentration range, long steady-state times and the toxicity of the process. The alternative nitrosation/nitration assays omit the coupling with the second component,[20] though colour changes are not so evident, especially when trying to detect trace amounts, and noxious *N*-nitrosamines are formed in some cases. Consequently, the development of on-site tests for naked-eye nitrite detection that are fast, straightforward, efficient in different concentration ranges and that might be carried out both in solution and in other types of media is welcome.

By virtue of our current interest in indolizine chemistry,[21] we present herein the first application of the Eschenmoser's salt,[22] a commercially available and well-known (dimethylamino)methylating chemical, as a direct formylating agent, which allows the regioselective formylation of indolizines. Moreover, the resulting indolizinecarbaldehydes have found application in the synthesis of some push-pull dyes and in the selective and efficient colorimetric detection of the nitrite ion.

Results and Discussion

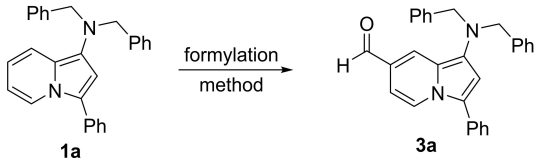
The starting indolizines **1** (Scheme 1) were prepared following our reported multicomponent method from indolizine-2-carbaldehyde, secondary amines and terminal alkynes, catalysed by copper nanoparticles on activated carbon.[21a] An initial study on indolizine formylation was conducted using indolizine **1a** as a model substrate. Given the low volatility of the potential products and the fact that they are colored, we found TLC as a fast and reliable tool for reaction monitoring (Figure S1). Attempts to formylate indolizine **1a** using conventional methods were unfruitful (Table 1, entries 1–4; Figure S2).

Fortunately, when exploring the (dimethylamino)methylation reagents (Table 1, entries 5 and 6), the corresponding carbaldehyde **3a** was formed after reaction with the Eschenmoser's salt (Table 1, entry 6), albeit in poor yield. An exhaustive optimization process was undertaken in order to improve the performance of this transformation. For this purpose, numerous experiments were carried out by varying the solvent, base, stoichiometry, amount of water, atmosphere and reaction time (Figures S3–S10). The best conditions were determined to be: **1a**/Eschenmoser's salt (**2**)/$NaHCO_3$ (1:2:2) in MeCN and air at rt for 8 h.



Scheme 1. Multicomponent synthesis of indolizines **1**.

Table 1: Preliminary attempts to formylate indolizine **1a**.



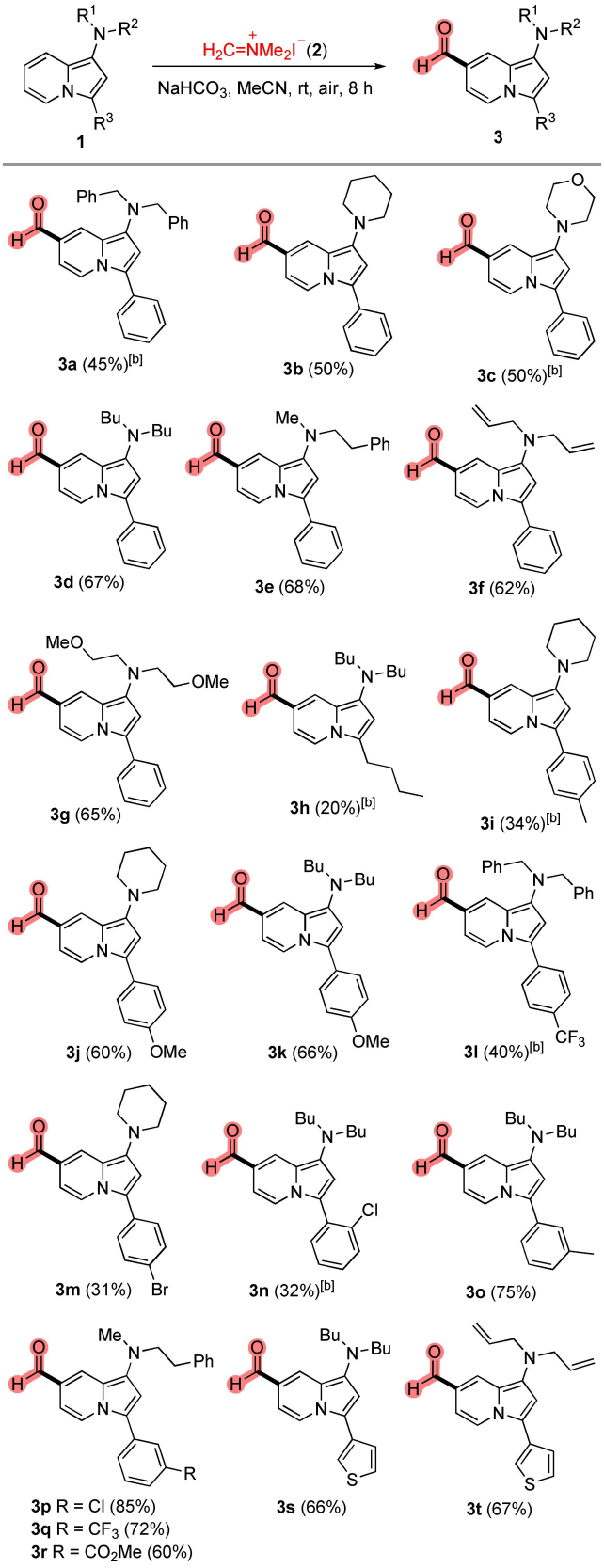
Entry	Method	Formation of **3a**
1	Duff[23] (HMTA, CF_3CO_2H)	x[a]
2	Reimer-Tiemann[6a] ($CHCl_3$, KOH, H_2O)	x[a]
3	Vilsmeier–Haack[24] (DMF, $POCl_3$, DCE)	x[a]
4	i) BuLi-TMEDA, THF; ii) DMF[25]	x[a]
5	HCHO + Me_2NH,[b] MeCN[26][	x[a]
6	$H_2C{=}NMe_2I$ (**2**),[b,c] MeCN	✓[d]

[a] No formylation product was detected. [b] (Dimethylamino)methylating reagent. [c] Eschenmoser's salt. [d] Solely this method led to a formylated product (**3a**, in this case), though in < 10% isolated yield.

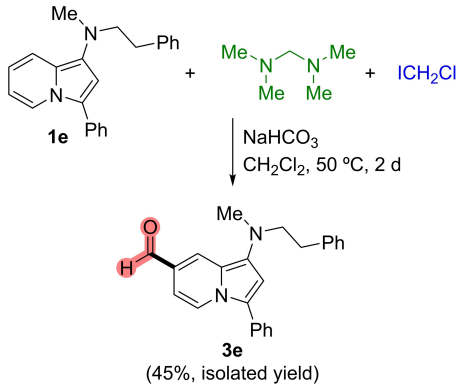
The optimized formylation conditions were extended to an array of indolizines derived from seven different secondary amines and twelve different alkynes (Table 2). In general, the reactivity of the starting indolizines seems to be more dependent on the electronic character of the substituent at the 3 position, rather than on the 1-amino substituent, though dibenzylamino-substituted indolizines were comparatively less reactive (**3a** and **3l**). The 3-alkyl-substituted indolizine **3h** was found to be the most reluctant to react. Substituents with a negative inductive effect at the *ortho* and *para* positions of the 3-aryl unit also manifested a detrimental effect, with warming being recommended to improve the yield (**3l**–**3n**). On the contrary, moderate-to-good yields were recorded for phenyl- (**3b**–**3g**) and 4-methoxyphenyl-substituted (**3j** and **3k**) indolizines, in the latter case probably due to a positive resonant effect exerted by the methoxy group. All the *meta*-substituted 3-aryl indolizines were formylated in good yields (**3o**–**3r**), irrespective of the electronic character of the substituent; similar behavior was observed for the thienyl-substituted indolizines **3s** and **3t**. It is noteworthy that the reaction was regioselective in all the cases studied, with the formyl group being incorporated exclusively into the 7 position of the indolizine nucleus. Moreover, we managed to adapt a protocol for the in situ generation of the Eschenmoser's salt (**2**), from *N,N,N′,N′*-tetramethylmethanediamine and chloroiodomethane,[27] and subsequent formylation of the indolizine (Scheme 2); lower isolated yield and longer reaction time were noted when compared with the use of the Eschenmoser's salt, though it can be considered a fair alternative method.[28]

A series of experiments were conducted in order to shed light on the reaction mechanism. A first evidence was given by the reaction of the indolizine **1u** with the Eschenmoser's salt (**2**), which gave the substituted indolizine **4** (Scheme 3); this was indeed the only indolizine tested in which the (dimethylamino)methylated product was obtained instead of the formylated one. Next, we tried to ascertain the source of the oxygen atom in the formyl group. We observed a progressive and significant decrease in the conversion of indolizines **1a** (Figure S8) and **1b** (Figure 2a), when increasing the amount of water in the formylation with **2**. This behavior could be in agreement with water being formed as a by-product, the addition of which to the reaction medium would be unfavorable to displace the reaction to the desired product; an explanation based on the loss of activity of **2** by the reaction with water cannot be ruled out.[22b] When the formylation of **1b** was carried out in the presence of 1 equiv $H_2{}^{18}O$ under an atmosphere of dry synthetic air, the incorporation of ^{18}O into the product **3b** was 19 % (Figures 2b and S11). This relatively low incorporation is not so much unexpected if we take into account that the substitution of ^{18}O from $H_2{}^{18}O$ into carbonate oxyanions (i.e., $HC^{16}O_3^-$ and $C^{16}O_3^{2-}$) is feasible.[29] The reactivity of indolizines **1a** and **1b** towards the formylation dramatically dropped when the reaction was carried out in dry and degassed MeCN under argon (Scheme 4a, Figures S9 and S12). In the case of **1b** (*m/z* 276), a by-product was observed by GC-MS, which *m/z* (274) suggests that oxidation of the starting indolizine occurred (Figure S12). Astonishingly, we

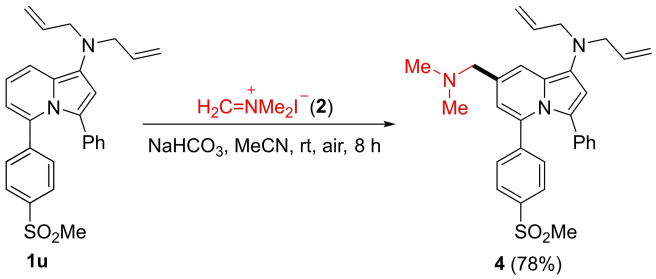
Table 2: Formylation of indolizines **1** with the Eschenmoser's salt (**2**).[a]



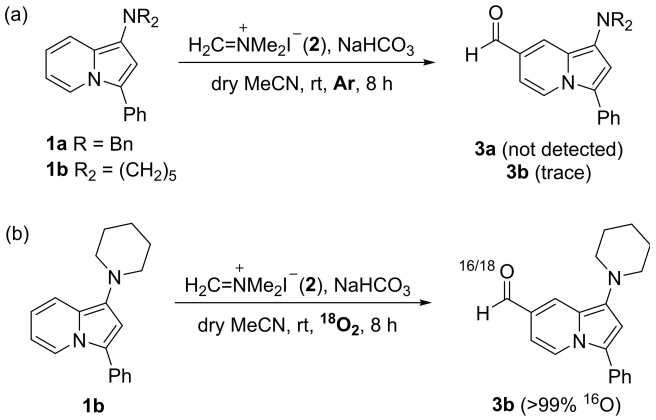
[a] **1** (1.0 mmol), **2** (2.0 mmol), $NaHCO_3$ (2.0 mmol), MeCN, air, 8 h; yield of the isolated product **3** in parenthesis. [b] Reaction at 70 °C.



Scheme 2. Formylation of indolizine **1e** by in situ generation of the Eschenmoser's salt.



Scheme 3. Reaction of indolizine **1u** with the Eschenmoser's salt (**2**).



Scheme 4. Reaction of indolizines **1a** and **1b** with the Eschenmoser's salt (**2**) using degassed and dry MeCN under (a) Ar and (b) $^{18}O_2$ atmospheres.

did not observe any appreciable incorporation of ^{18}O when indolizine **1b** was subjected to the standard conditions but under a $^{18}O_2$ atmosphere (Scheme 4b and Figure S13). Therefore, the above experiments sustain that the (dimethylamino)methylated indolizine is the most probable intermediate, and that the molecular oxygen of air is not the source of the oxygen atom in the formyl group of the products but the bicarbonate anion.[30] In fact, if we take into consideration the 2 equiv of $NaHCO_3$ and 1 equiv of $H_2{}^{18}O$ as the only sources of O in the experiment of Figure 2b, the expected ^{18}O incorporation after total isotope scrambling should be 14 %, which is close to that determined experimentally (19 %). A reaction mechanism was proposed involving: (a) a Friedel–Crafts-type reaction between the indolizine (**1**) and the Eschenmoser's salt (**2**), through the dienamine moiety of **1**, to form an iminium ion; (b) base-promoted rearomatization to give the Eschenmoser's product; (c) oxidation of the latter by the oxygen of air to generate a (dimethyl)iminium ion, with the concomitant release of water; (d) addition of water to the latter iminium ion leading to a hemiaminal; (e) simultaneous liberation of dimethylamine and formation of the C=O bond; and (f) final neutralization by the action of $NaHCO_3$ and/or Me_2NH (Scheme 5). The fact that better formylation yields are attained when utilizing two equivalents of the Eschenmoser's salt and two equivalents of $NaHCO_3$ could be related with the former being partially deactivated by the reaction with the in situ generated water; the HI derived from this side reaction and/or the formylation reaction could be neutralized by the extra amount of $NaHCO_3$. The results in Table 2 lend weight to the argument that the oxidation step could be more favoured when an electron-rich aromatic or heteroaromatic substituent is present at the 3 position of the indolizine; the opposite can be argued when that substituent is alkyl or electron-poor.

In view of the potential use of the Eschenmoser's salt as a general formylation tool, and considering that the oxidation by air of the intermediate (dimethylamino)methylated product might not be so spontaneous as for compounds in Table 2, three model starting materials were additionally included in this study: a nitrogen heteroaromatic (indole), an oxacyclic one (3,4-dihydro-2*H*-pyran) and an aromatic one (*N*,*N*-dimethylaniline). The three compounds reacted nicely with the Eschenmoser's salt to give the (dimethylamino)methylated products, but the aldehyde was not detected except in the case of *N*,*N*-dimethylaniline and in a small amount (< 10 %), thus making necessary the addition of an oxidant besides air. Our recent interest on the selective oxidation of amines,[31] led us to combine the Eschenmoser's salt with some of our catalysts; that of copper nanoparticles on activated carbon (CuNPs/C) was found to be efficient in this transformation, giving rise to the expected aldehydes **5**–**7** in moderate-to-good isolated yields (Scheme 6).

Taking into account the importance of indolizines in materials science, relevant to their notable photophysical properties, we took advantage of the versatility of the formyl group in indolizines **3** to extend their conjugation and obtain some push-pull dyes (Scheme 7).[32] Horner–Wadsworth–Emmons reaction of indolizine **3b** with diethyl (cyanomethyl)phosphonate led to the *β*-indolizinyl acrylonitrile **8** in high yield. Condensation of **3b** with an excess of acetone furnished the methyl indolizinylvinyl ketone **9** in nearly quantitative yield, whereas the application of these conditions to the double condensation of **3b** with acetone was less efficient. Fortunately, this apparent lower reactivity could be circumvented by warming under ultrasound activation, to produce **10** in a fair isolated yield.

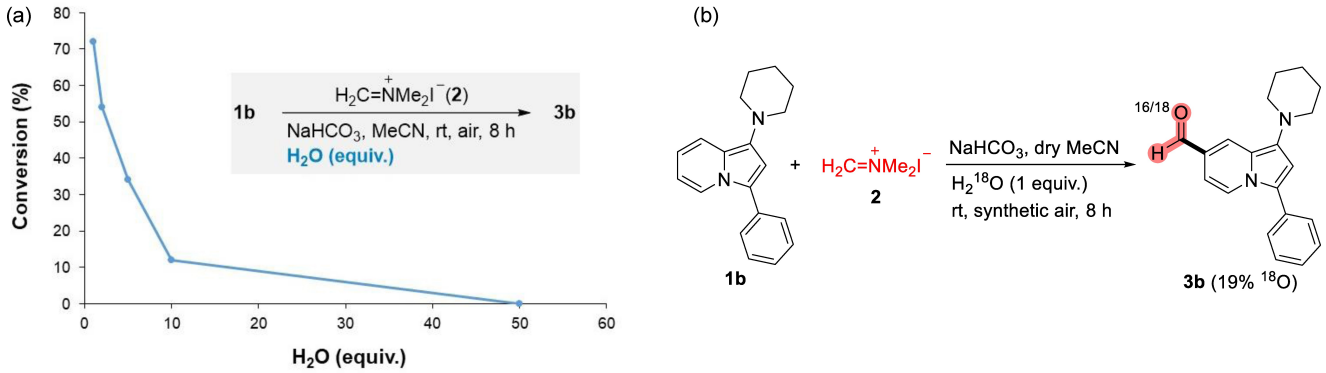
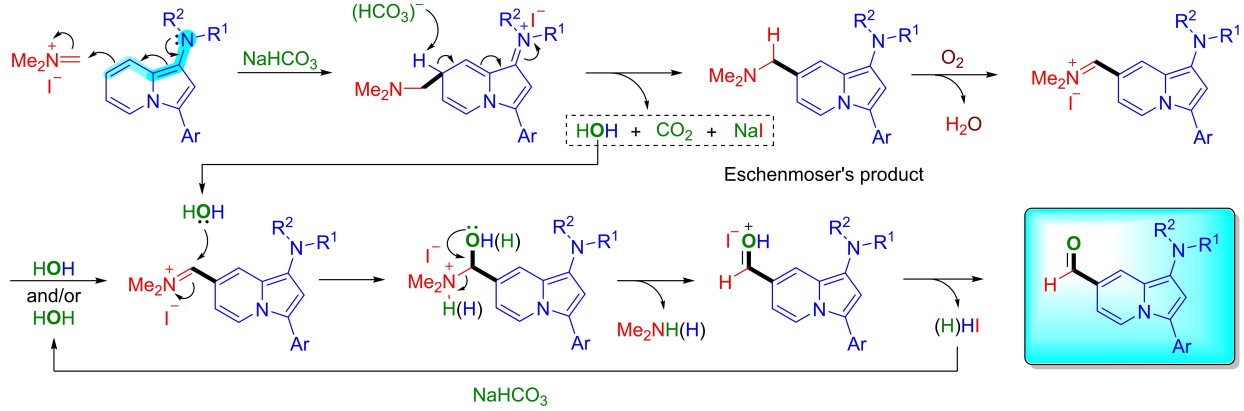
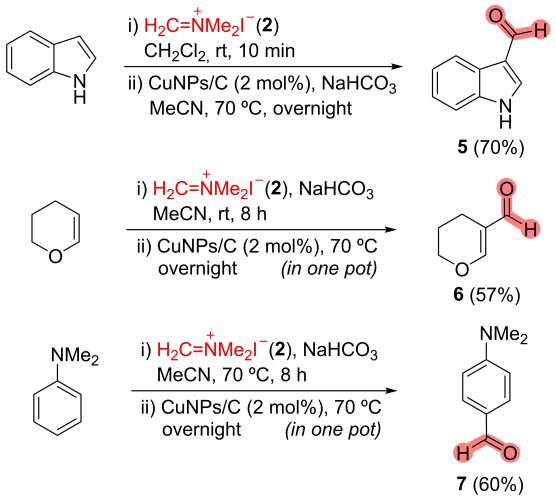


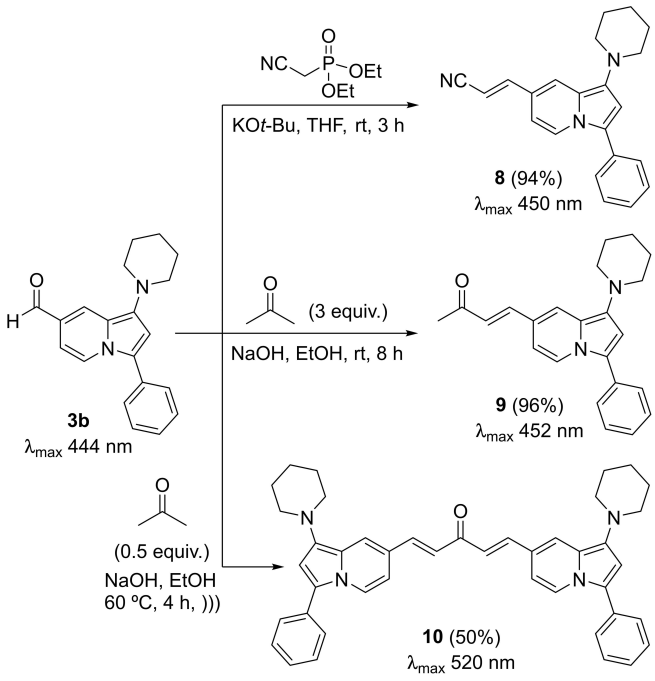
Figure 2. (a) Effect of the amount of added water in the formylation of **1 b** with **2**. (b) Experiment with labeled water in the formylation of **1 b** with **2**.



Scheme 5. General reaction mechanism proposed for the formylation of indolizines **1** with the Eschenmoser's salt (**2**).



Scheme 6. Application of the Eschenmoser's salt to the formylation of other substrates.



Scheme 7. Transformation of indolizine **3 b** into some push-pull dyes.

Furthermore, we observed that indolizinecarbaldehydes **3**, in a proper reaction medium, could be used for the colorimetric detection of nitrite ion:[33] when solutions of **3 a** or **3 b** (10^{-4} M, MeCN) in acidic medium were mixed with a solution of nitrite ion (10^{-4} M, MeCN), a change in color

from pale yellow to deep red occurred immediately. We must underline that, when the same protocol was applied to the parent indolizine **1a**, the detection of nitrite was not effective because the color change was hardly discernible, especially, when compared with that of indolizinecarbaldehyde **3a** (Figure S14). The test was found to be highly selective for nitrite ion against other thirteen anions, including both inorganic and organic ones (Figure 3a). This selectivity was also manifested when compared with its closest relative, the nitrate ion (Figure 3b). By varying the amount and concentration of indolizine **3a**, acid (2N HCl) and nitrite, we could conclude that the color change is fast for nitrite concentrations $\geq 10^{-4}$ M. For nitrite concentrations $< 10^{-4}$ M, the addition of some solid NaCl considerably accelerated the reaction and the consequent color change.[20a] In this way, the test was successfully applied to the detection of 3 ppm of aqueous $NaNO_2$ (4.35×10^{-5} M), an amount set by the World Health Organization as a safe limit in drinking water, as well as in detecting the maximum amount of nitrite in drinking water set by the EPA (1 ppm, 1.45×10^{-5} M).[34] We must point out that the identification of nitrite in solutions in the range 10^{-2}–10^{-5} M could be effected with very diluted solutions of the indolizine **3a**, typically $< 10^{-4}$ M (Table S1); this fact gives an idea on the sensitivity of **3a** and sustainability of the assay.

UV/Vis spectroscopy analysis brought into view very different spectra for **3a**, **3a**/2N HCl and **3a**/2N HCl/NO_2^-, with λ_{max} of 434, 385 and 509 nm, respectively (Figure S15a). A similar pattern was observed for **3d**, **3d**/2N HCl and **3d**/2N HCl/NO_2^-,[35] with λ_{max} of 444, 385 and 532 nm, respectively (Figures 4 and S15b). The latter was used to establish the relationship between the absorbance and nitrite concentration, displaying a linear correlation in the three different concentration ranges recorded (Figures 5 and S16). The LoD[36] and LoQ[37] were determined to be 3.04×10^{-6} M and 1.01×10^{-5} M, respectively (Figure S16c and equations below).[38]

In search for an assay on a solid support, 10^{-4} M samples of **3d** were impregnated on SiO_2, flash SiO_2 and Amberlyst MB 3A, with acidification (2N HCl) of a 10^{-2} M nitrite solution and mixing; impregnation of **3d** on basic Al_2O_3, Celite, microcrystalline cellulose, $MgSO_4$, MgO, NaCl, ZnO, CaO, TiO_2, PVA, PVC and montmorillonite K-10 was done with or without previous acidification of **3d** (the nitrite solution was acidified in the latter case), followed by addition of the nitrite solution. Only SiO_2, flash SiO_2, microcrystalline cellulose, $MgSO_4$ and PVA underwent a color change, with the three latter being acidified prior to the impregnation with **3d**. Unfortunately, the reaction was slow and with a faint coloration, making these assays useless for lower nitrite concentrations. Last attempts were carried out on cotton swabs as supports by (a) immersion of the swab into a 10^{-4} M solution of **3d**, drying for a few minutes and subsequent introduction into an acidified 10^{-2} M nitrite solution; (b) immersion of the swab into a previously acidified **3d** solution and, once dry, immersion into the nitrite solution; and (c) immersion of the swab into the nitrite solution, followed by drying and immersion in an acidified solution of **3d**. Luckily, the third variant of the experiment produced a noticeable color change both in the cotton swab and in the solution (Figure 3c). This change is

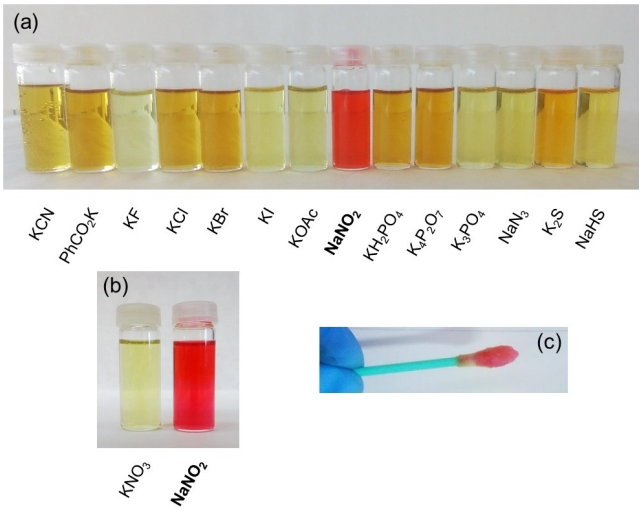


Figure 3. Test for the selective detection of nitrite ion (10^{-4} M, MeCN) using **3a** (10^{-4} M, MeCN) in acidic medium (pH 1.57, 2N HCl): (a) in solution against thirteen anions (10^{-4} M, MeCN or 1:1 MeCN-H_2O); (b) in solution against KNO_3 (10^{-4} M, MeCN); (c) on a cotton swab.

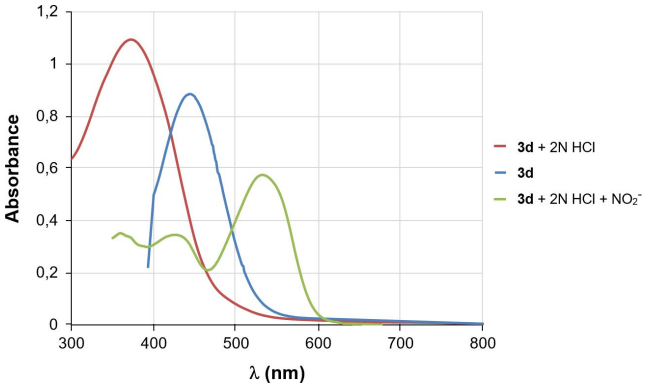


Figure 4. UV/Vis spectroscopy analysis of **3d**, **3d**/2N HCl and **3d**/2N HCl/NO_2^-.

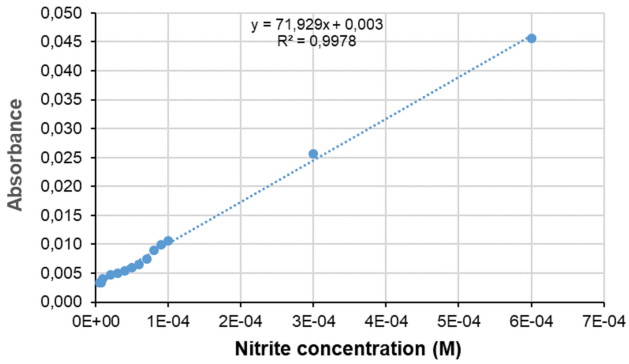


Figure 5. Calibration curve for nitrite concentrations ranging from 6×10^{-4} to 5×10^{-6} M using indolizine **3d** (λ 532 nm).

relatively fast for concentrations of nitrite in the range $>10^{-2}$–10^{-3} M. As occurred in solution, the addition of NaCl is necessary for nitrite concentrations $<10^{-4}$ M, together with a higher concentration of the indolizine **3d** (10^{-3} M) and acid. Nonetheless, we would recommend the cotton swab assay to be applied for nitrite concentrations of up to 10^{-4} M, because the pink color is more difficult to be noticed for lower concentrations. As mentioned in the introduction, sodium nitrite is a common preservative used in charcuterie and other food products (E250); gratifyingly, we could extend the test to the detection of nitrite in frankfurters, after previous extraction with warm water (Supporting Information).

Conclusion

This study has highlighted the application of the Eschenmoser's salt, a common (dimethylamino)methylene building block in organic synthesis, as a novel direct formylation agent in the presence of sodium bicarbonate. When applied to 1-amino-substituted indolizines, the corresponding indolizine-7-carbaldehydes are formed in a regioselective manner and in modest-to-good yields. The procedure is very simple, involving two solid reagents, in air at room temperature, and compatible with the presence of amino groups, among others. It must be pointed up that the classical formylation methods were found to be inefficient in this transformation. A thorough mechanistic study has revealed, against all odds, that the source of the oxygen atom in the formyl group is not the molecular oxygen of air but bicarbonate anion. We have also demonstrated that the Eschenmoser's salt can be used to install a formyl group in other substrates, albeit the addition of an oxidant or catalyst (e.g., CuNPs/C) can be mandatory to facilitate the oxidation step of the (dimethylamino)methylated intermediate. Taking advantage of the presence of the formyl group, some push-pull dyes have been synthesized by extending the indolizine-ring conjugation.

In addition, the indolizinecarbaldehydes obtained have been shown to be selective agents for the rapid and efficient colorimetric detection of nitrites in solution for a broad variety of concentrations. Further to this, the nitrite ion can be also naked-eye discerned on a simple cotton swab. Good results have been observed for the nitrite ion detection both in water and in different food. The development of a portable nitrite detection kit is under way.

Acknowledgements

This work was generously supported by the Spanish Ministerio de Ciencia e Innovación (MCIN; grant no. CTQ2017-88171-P), the Generalitat Valenciana (GV; grants no. AICO/2017/007 and APOTIP/2021/018), and the Instituto de Síntesis Orgánica (ISO). T. A.-C. thanks the Vicerectorado de Investigación of the Universidad de Alicante for a grant (no. UAFPU20-02). We are very grateful to María José González-Soria and Reni Nikolova for performing some preliminary experiments.

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Aldehydes · Analytical Methods · Formylation · Indolizines · Nitrite Detection

[1] Recent reviews: a) L. Guillemard, N. Kaplaneris, L. Ackermann, M. J. Johansson, *Nat. Chem. Rev.* **2021**, *5*, 522–545; b) B. Zhao, B. Prabagar, Z. Shi, *Chem* **2021**, *7*, 2585–2634; c) U. Dutta, S. Maiti, T. Bhattacharya, D. Maiti, *Science* **2021**, *372*, eabd5992; d) L. Zhang, T. Ritter, *J. Am. Chem. Soc.* **2022**, *144*, 2399–2414.

[2] Special volume on aldehydes: *Science of Synthesis, Vol. 25* (Ed.: R. Brückner), Thieme, Stuttgart, **2007**.

[3] a) L. Tang, G. Wei, R. Nandhakumar, Z. Guo, *Bull. Korean Chem. Soc.* **2011**, *32*, 3367–3371; b) Y. Zhou, J. Yoon, *Chem. Soc. Rev.* **2012**, *41*, 52–67; c) H. S. Jung, X. Chen, J. S. Kim, J. Yoon, *Chem. Soc. Rev.* **2013**, *42*, 6019–6031; d) F. Wang, L. Wang, X. Chen, J. Yoon, *Chem. Soc. Rev.* **2014**, *43*, 4312–4324.

[4] a) G. Olah, L. Ohannesian, M. Arvanaghi, *Chem. Rev.* **1987**, *87*, 671–686; b) M. B. Smith, *March's Advanced Organic Chemistry. Reactions, Mechanisms and Structure, 7th Edn.*, Wiley, Hoboken, **2013**, pp. 625–628.

[5] Reviews: a) O. Meth-Cohn, S. P. Stanforth in *Comprehensive Organic Synthesis, Vol. 2* (Eds.: B. M. Trost, I. Fleming), Pergamon Press, Oxford, **1991**, pp. 777–794; b) N. Zhang, D. Dong in *Science of Synthesis, C-1 Building Blocks in Organic Synthesis, Vol. 2* (Ed. P. W. N. M. Van Leeuwen), Thieme, Stuttgart, **2014**, pp. 333–347.

[6] Reviews: a) H. Wynberg, E. W. Meijer, *Org. React.* **1982**, *28*, 1–36; b) H. Wynberg in *Comprehensive Organic Synthesis, Vol. 2* (Eds.: B. M. Trost, I. Fleming), Pergamon Press, Oxford, **1991**, pp. 769–775.

[7] See, for instance: a) J. C. Duff, E. J. Bills, *J. Chem. Soc.* **1932**, 1987–1988; b) F. Jović, A. Sucec, I. Nekola, D. Cavuzic, E. Marcelic, E. Mestrovic, *Org. Process Res. Dev.* **2015**, *19*, 1268–1273.

[8] a) H. Heaney in *Comprehensive Organic Synthesis, Vol. 2* (Eds.: B. M. Trost, I. Fleming), Pergamon Press, Oxford, **1991**, pp. 749–752; b) M. Tanaka, M. Fujiwara, Q. Xu, Y. Souma, H. Ando, K. K. Laali, *J. Am. Chem. Soc.* **1997**, *119*, 5100–5105.

[9] C. Zhu, T. Pinkert, S. Greßies, F. Glorius, *ACS Catal.* **2018**, *8*, 10036–10042.

[10] S. M. Bronner, G.-Y. J. Im, N. K. Garg, in *Heterocycles in Natural Product Synthesis* (Eds.: K. C. Majumdar, S. K. Chattopadhyay), Wiley-VCH, Weinheim, **2011**, pp. 221–265.

[11] Reviews: a) V. R. Vemula, S. Vurukonda, C. K. Bairi, *Int. J. Pharm. Sci. Rev. Res.* **2011**, *11*, 159–163; b) G. S. Singh, E. E. Mmatli, *Eur. J. Med. Chem.* **2011**, *46*, 5237–5257; c) V. Sharma, V. Kumar, *Med. Chem. Res.* **2014**, *23*, 3593–3606; for a recent article, see: d) I. Baussanne, O. Firstova, A. B. Dediu, C.

Larosa, B. Furdui, I. O. Ghinea, A. Thomas, S. Chierici, R. Dinica, M. Demeunynck, *Bioorg. Chem.* **2021**, *116*, 105390.

[12] See, for instance: a) A. Rotaru, I. Druta, E. Avram, R. Danac, *Arkivoc* **2009**, *xiii*, 287–299; b) B. Liu, Z. Wang, N. Wu, M. Li, J. You, J. Lan, *Chem. Eur. J.* **2012**, *18*, 1599–1603; c) Y. R. Song, C. V. Limb, T. W. Kima, *Luminescence* **2016**, *31*, 364–371; d) C. R. S. Bertallo, L. S. Berlim, D. S. Olivier, T. R. Arroio, A. S. Ito, G. C. Clososki, *Dyes Pigm.* **2022**, *198*, 109996; e) T. Kim, J. Kim, *Molecules* **2022**, *27*, 12; f) J. S. A. Badaro, B. Koszarna, M. H. E. Bousquet, E. T. Ouellette, D. Jacquemin, D. T. Gryko, *Org. Chem. Front.* **2022**, *9*, 1861–1874.

[13] a) J. Adovelande, J. Delèze, J. Schrével, *Biochem. Pharmacol.* **1998**, *55*, 433–440; b) W. Huang, T. Zuo, X. Luo, H. Jin, Z. Liu, Z. Yang, X. Yu, L. Zhang, L. Zhang, *Chem. Biol. Drug Des.* **2013**, *81*, 730–741; c) S. Hagishita, M. Yamada, K. Shirahase, T. Okada, Y. Murakami, Y. Ito, T. Matsuura, M. Wada, T. Kato, M. Ueno, Y. Chikazawa, K. Yamada, T. Ono, I. Teshirogi, M. Ohtani, *J. Med. Chem.* **1996**, *39*, 3636–3658; d) D. A. James, K. Koya, H. Li, G. Liang, Z. Xia, W. Ying, Y. Wu, L. Sun, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1784–1787; e) A. V. Aksenov, N. A. Arutiunov, N. K. Kirilov, D. A. Aksenov, I. Y. Grishin, N. A. Aksenov, H. Wang, L. Du, T. Betancourt, S. C. Pelly, A. Kornienko, M. Rubin, *Org. Biomol. Chem.* **2021**, *19*, 7234–7245; f) Y.-M. Shen, P.-C. Lv, W. Chen, P.-G. Liu, M.-Z. Zhang, H.-L. Zhu, *Eur. J. Med. Chem.* **2010**, *45*, 3184–3190; g) A. I. Nasir, L.-L. Gundersen, F. Rise, O. Antonsen, T. Kristensen, B. Langhelle, A. Bast, I. Custers, G. R. M. M. Haenen, H. Wikström, *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1829–1832; Recent application to treat prostate cancer: h) Q. Xiang, C. Wang, T. Wu, C. Zhang, Q. Hu, G. Luo, J. Hu, X. Zhuang, L. Zou, H. Shen, X. Wu, Y. Zhang, X. Kong, J. Liu, Y. Xu, *J. Med. Chem.* **2022**, *65*, 785–810.

[14] a) R. Sarkar, T. Chaudhuri, A. Karmakar, C. Mukhopadhyay, *Org. Biomol. Chem.* **2015**, *13*, 11674–11686; b) A. S. K. Raj, K.-C. Tan, L.-Y. Chen, M.-J. Cheng, R.-S. Liu, *Chem. Sci.* **2019**, *10*, 6437–6442; c) M. Gong, J. Guo, P. Jiang, Y. Zhang, Z. Fu, W. Huang, *Chem. Asian J.* **2020**, *15*, 352–355.

[15] Regulation (EC) No 1333/2008 of the European Parliament and of The Council on food additives, Dec. 2008.

[16] Reviews: a) N. S. Bryan, D. D. Alexander, J. R. Coughlin, A. L. Milkowski, P. Boffetta, *Food Chem. Toxicol.* **2012**, *50*, 3646–3665; b) M. Parvizishad, A. Dalvand, A. H. Mahvi, F. Goodarzi, *Health Scope* **2017**, *6*, e14164; c) F.-X. Zhang, Y. Miao, J.-G. Ruan, S.-P. Meng, J.-D. Dong, H. Yin, Y. Huang, F.-R. Chen, Z.-C. Wang, Y.-F. Lai, *Med. Sci. Monit.* **2019**, *25*, 1788–1799; d) See, also: J. Mélin, "Use of sodium nitrite in food", Parliamentary question for written answer E-005806/2020 to the Commission, can be found under https://www.europarl.europa.eu/doceo/document/E-9-2020-005806 EN.html, **2020**.

[17] Reviews: a) J. Dutt, J. Davis, *J. Environ. Monit.* **2002**, *4*, 465–471; b) P. Singh, M. K. Singh, Y. R. Beg, G. R. Nishad, *Talanta* **2019**, *191*, 364–381; c) M. Sepahvand, F. Ghasemi, H. M. Seyed Hosseini, *Food Chem. Toxicol.* **2021**, *149*, 112025.

[18] See, for instance: a) N. Adarsh, M. Shanmugasundaram, D. Ramaiah, *Anal. Chem.* **2013**, *85*, 10008–10012; b) D. Viboonratanasri, S. Pabchanda, P. Prompinit, *Appl. Surf. Sci.* **2018**, *440*, 1261–1268; c) Z. Xu, W. Shi, C. Yang, J. Xu, H. Liu, J. Xu, B. Zhu, *Luminescence* **2020**, *35*, 299–304; d) L. C. Murfin, C. M. López-Alled, A. C. Sedgwick, J. Wenk, T. D. James, S. E. Lewis, *Front. Chem. Sci. Eng.* **2020**, *14*, 90–96; e) M. Wang, P. Liu, H. Zhu, B. Liu, X. Niu, *Biosensors* **2021**, *11*, 280.

[19] See, for instance: a) J. P. Griess, *Ber. Dtsch. Chem. Ges.* **1879**, *12*, 426–428; b) J. Nama, I.-B. Jung, B. Kim, S.-M. Lee, S.-E. Kim, K.-N. Lee, D.-S. Shin, *Sens. Actuators B* **2018**, *270*, 112–118; c) H. Wu, X. Shen, D. Huoa, Y. Ma, M. Bian, C. Shen, C. Houa, *Spectrochim. Acta Part A* **2020**, *225*, 117470; d) J. Hou, H. Wu, X. Shen, C. Zhang, C. Hou, Q. He, D. Huo, *Sensors* **2020**, *20*, 1501.

[20] See, for instance: a) M. González-Jiménez, J. Arenas-Valgañón, I. F. Céspedes-Camacho, J. C. García-Prieto, E. Calle, J. Casado, *J. Chem. Educ.* **2013**, *90*, 1053–1056; b) F. Zhang, X. Zhu, Z. Jiaoa, X. Liu, H. Zhang, *Spectrochim. Acta Part A* **2018**, *200*, 275–280; c) K. Vellingiri, V. Choudhary, L. Philip, *J. Environ. Chem. Eng.* **2019**, *7*, 103374; d) K. Gayen, S. Paul, S. Hazra, A. Banerjee, *Langmuir* **2021**, *37*, 9577–9587.

[21] a) M. J. Albaladejo, F. Alonso, M. J. González-Soria, *ACS Catal.* **2015**, *5*, 3446–3456; b) M. J. Albaladejo, M. J. González-Soria, F. Alonso, *J. Org. Chem.* **2016**, *81*, 9707–9717; c) M. J. Albaladejo, M. J. González-Soria, F. Alonso, *Green Chem.* **2018**, *20*, 701–712; d) M. J. González-Soria, F. Alonso, *Adv. Synth. Catal.* **2019**, *361*, 5005–5017.

[22] a) J. Schreiber, H. Maag, N. Hashimoto, A. Eschenmoser, *Angew. Chem. Int. Ed. Engl.* **1971**, *10*, 330–331; *Angew. Chem.* **1971**, *83*, 355–357; b) E. F. Kleinman in *Encyclopedia of Reagents for Organic Synthesis, Vol. 3* (Ed.: L. Paquette), Wiley, Chichester, **1995**, pp. 2090–2093; for recent applications of the Eschenmoser's salt, see: c) D. Kaiser, V. Tona, C. R. Gonçalves, S. Shaaban, A. Oppedisano, N. Maulide, *Angew. Chem. Int. Ed.* **2019**, *58*, 14639–14643; *Angew. Chem.* **2019**, *131*, 14781–14785; d) M. Lemmerer, M. Riomet, R. Meyrelles, B. Maryasin, L. González, N. Maulide, *Angew. Chem. Int. Ed.* **2022**, *61*, e202109933; *Angew. Chem.* **2022**, *134*, e202109933; e) H. Zheng, K. Wang, I. Faghihi, W. P. Griffith, H. Arman, M. P. Doyle, *ACS Catal.* **2021**, *11*, 9869–9874.

[23] W. E. Smith, *J. Org. Chem.* **1972**, *37*, 3972–3973.

[24] M. Zhang, X. He, S. Li, Y. Shang, *Heterocycles* **2018**, *96*, 2079–2086.

[25] A. G. Kuznetsov, A. A. Bush, V. B. Rybakov, E. V. Babaev, *Molecules* **2005**, *10*, 1074–1083.

[26] T. A. Bryson, G. H. Bonitz, C. J. Reichel, R. E. Dardis, *J. Org. Chem.* **1980**, *45*, 524–531.

[27] S. Miyano, H. Hokari, H. Hashimoto, *Bull. Chem. Soc. Jpn.* **1982**, *55*, 534–539.

[28] An exhaustive optimization of the reaction conditions was not conducted in this case. Therefore, the obtained yield is susceptible of improvement under other related conditions.

[29] H. E. King, T. Geisler, *Minerals* **2018**, *8*, 158.

[30] We have observed the condensation of drops of water in the upper part of the reaction tube when the formylation takes place, but not when it fails. If this water is derived from the reaction of O_2 with the Eschenmoser's product at the liquid–gas interface, the water derived from $NaHCO_3$ in the rearomatization step could react preferentially with the iminium ion intermediate, thus supporting the fact that $NaHCO_3$ is the main source of oxygen in the formyl group of the products.

[31] a) I. Martín-García, G. Díaz-Reyes, G. Sloan, Y. Moglie, F. Alonso, *J. Mater. Chem. A* **2021**, *9*, 11312–11322; b) M. Yaghmaei, M. Villanueva, I. Martín-García, F. Alonso, X. Zhang, N. Joshi, A. E. Lanterna, J. Scaiano, *Photochem. Photobiol. Sci.* **2022**, *21*, 1473–1479.

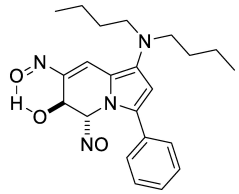
[32] For recent examples of highly conjugated indolizine dyes and their properties, see: D. Ndaleh, C. Smith, M. L. Yaddehige, A. K. Shaik, D. L. Watkins, N. I. Hammer, J. H. Delcamp, *J. Org. Chem.* **2021**, *86*, 15376–15386, and the references therein. A manuscript on the photophysical properties of compounds **8**–**10** is in preparation.

[33] T. Antón-Cánovas, F. Alonso (Universidad de Alicante), WO 2021250296, **2021**.

[34] a) World Health Organization. *Guidelines for Drinking Water Quality*, incorporating 1st and 2nd addenda, *Vol. 1*, Recommendations, 3rd Edn.; WHO Press, Geneva, Switzerland, **2008**, pp. 417–419; b) M. J. Hill, *Nitrates and Nitrites in Food and Water*, 1st ed., Woodhead Publishing Limited, Hampshire, UK,

1996; c) United States Environmental Protection Agency. National Primary Drinking Water Regulations: Contaminant Specific Fact Sheets, Inorganic Chemicals, Consumer Version, USEPA, Washington, DC, **1995**.

[35] The isolation and structure elucidation of the substance responsible for the red color in **3d**/2N HCl/NO_2^- were found to be problematic. Nevertheless, the following structure has been proposed on the basis of the different analyses carried out (Supporting Information).



11

[36] Limit of Detection (LoD) is the lowest analyte concentration likely to be reliably distinguished from the highest apparent analyte concentration expected to be found when replicates of a blank sample containing no analyte are tested.

[37] Limit of Quantitation (LoQ) is the lowest concentration at which the analyte can be reliably detected.

[38] N. J. Miller, J. C. Miller, *Statistics and Chemometrics for Analytical Chemistry, 4th Edn.*, Pearson Education Ltd., London, **2000**, pp. 119–127.

Manuscript received: October 31, 2022
Accepted manuscript online: November 30, 2022
Version of record online: December 20, 2022