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Mendeleev Commun., 2024, **34**, 116–118

Mendeleev Communications

An efficient synthesis of substituted 4,5-dihydroxyimidazolidin-2-ones by oxidation of imidazolin-2-ones with HNO_3

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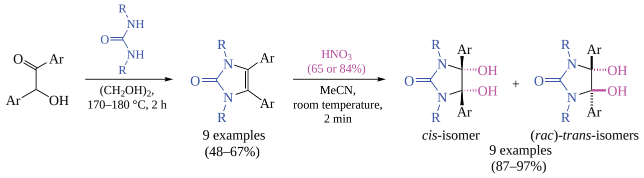
DOI: 10.1016/j.mencom.2024.01.035

Previously unavailable 1,3-dialkyl-4,5-diaryl-4,5-dihydroxy-imidazolidin-2-ones were obtained by the oxidation of 1,3-dialkyl-4,5-diaryl-4-imidazolin-2-ones with HNO_3 (65 or 84% aq.). The scope of required 4-imidazolin-2-ones obtained from acyloins has been expanded, which provided preparation of new representatives of the title compounds.



Keywords: 4,5-dihydroxyimidazolidin-2-ones, nitric acid, oxidation, 4-imidazolin-2-ones, diastereomers, acyloins, ureas.

Various 4,5-diaryl-4,5-dihydroxyimidazolidin-2-ones are patented as components for liquid crystal display devices,[1] polymers for evaluation of properties of composites based on softwood,[2] super-hydrophilic antibacterial coating sols,[3] superhydrophilic self-cleaning coating sols,[4] antimicrobial and antiviral compositions,[5] high-efficiency cationic modifiers for cotton fabrics,[6] efficient adhesives for plywood panels,[7] intermediates for the preparation of herbicides,[8] new types of androgen receptor degrading agents with high biological activity.[9] The reactivity of 4,5-dihydroxy-imidazolidin-2-ones (DHIs) is due to the presence of hemiacetal hydroxy groups, which makes it possible to transform them toward various mono- and bicyclic compounds, the products of replacement of these hydroxy groups (Figure 1).[10–19]

The synthesis of DHIs is multiply documented.[12,18–25] However, there are only two examples of the synthesis of 1,3-dialkyl-4,5-diaryl-substituted DHIs.[21–25] The most studied is the preparation of DHI **1a**, which is synthesized by the reaction of benzil **2a** with dimethylurea **3a** *via* refluxing in MeOH (or EtOH) in the presence of KOH (yield 85%),[21,22] or grinding in a mortar without a solvent (yield 91%),[23] and also upon oxidation of imidazolin-2-one **4a** with singlet oxygen in DMSO (yield 72%)[24] (Scheme 1). In addition, DHI **1′a** was synthesized from dimethylurea **3a** and 1,2-bis(4-bromophenyl)ethane-1,2-dione **2′a** by boiling in ethanol in the presence of EtONa (yield 61%).[25]

In this work, a new method for the preparation of 1,3-dialkyl-4,5-diaryl-substituted DHIs is developed. Anyway, it seemed

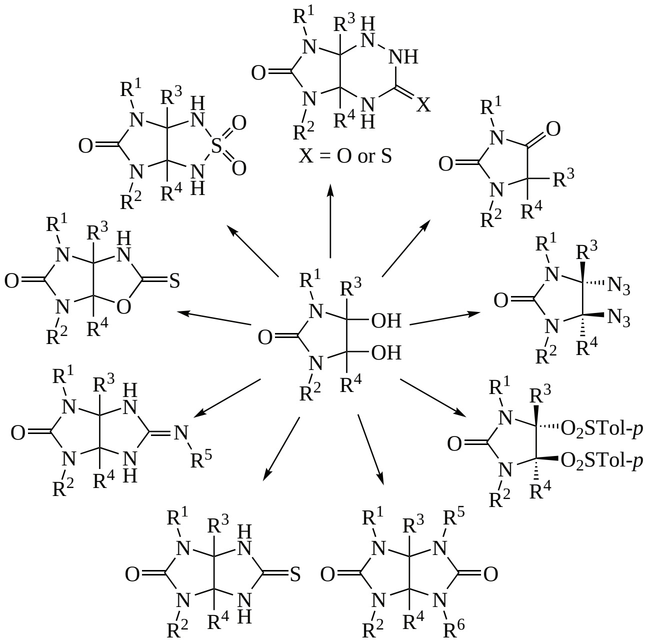
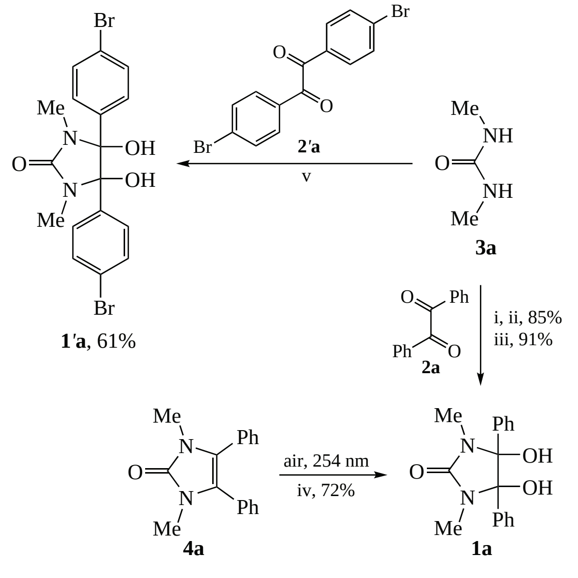
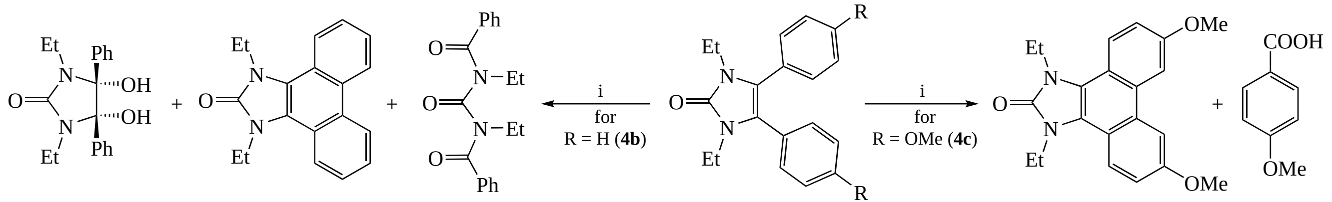


Figure 1 Heterocyclic structures synthesized from DHI.



Scheme 1 *Reagents and conditions*: i, EtOH, KOH (aq.), reflux, 2 h; ii, MeOH, KOH (aq.), reflux, 2 h; iii, solvent-free, grinding, 25 min; iv, DMSO, air, 254 nm, 45 °C, 12 h; v, EtOH (abs.), Na, reflux, 2 h.



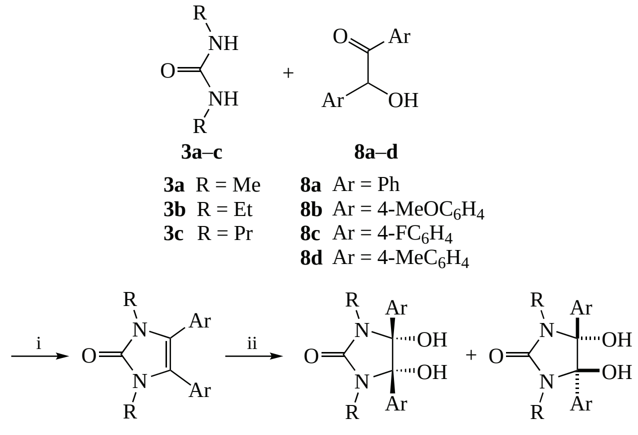
1b, 24% **5a**, 22% **6**, 5% **4b**,**c** **5b**, 46% **7**, 21%

Scheme 2 *Reagents and conditions*: i, DMSO, air, 254 nm, 70 h.

reasonable to examine the available methods involving other reactants. For this purpose, we checked the reactions of benzil **2a** with diethyl- and dipropylureas **3b**,**c**, as well as anisil **2b** with ureas **3a–c** under the conditions i,ii specified in Scheme 1 [i, MeOH, KOH (aq.), reflux, 2 h; ii, solvent-free, grinding for 25 min]. However, in these experiments only the starting reactants were isolated unchanged.

Therefore, we decided to study oxidation of imidazolin-2-ones **4b**,**c** with singlet oxygen generated from air under 254 nm UV irradiation using ^{1}H NMR monitoring (Scheme 2).[†] Monitoring the transformation of imidazolin-2-one **4b** showed that after 70 h the reaction practically stopped and further irradiation did not lead to significant changes in the product composition, while the conversion of starting **4b** was only 61%. As a result, the target DHI **1b** (only *cis*-isomer), 1,3-diethyl-1*H*-phenanthro[9,10-*d*]imidazol-2(3*H*)-one **5a** and *N*,*N'*-carbonylbis(*N*-ethylbenzamide) **6** were formed in a ratio of 4.65 : 3.78 : 1 (the yields were 24, 22 and 5%, respectively). The ratios of compounds were determined by the integral intensities of proton signals in the ^{1}H NMR spectra of the reaction mixtures: for **1b** 6.87–7.08 ppm [m, 10 H, CH(Ph)], for **4b** 7.19–7.40 ppm [m, 10 H, CH(Ph)], for **5a** 8.99 ppm (d, 2 H, CH, *J* = 7.4), for **6** 7.50 ppm [t, 2 H, CH(Ph), *J* = 7.4]. The formation of DHI did not occur when imidazolin-2-one **4c** was oxidized: after 70 h with 65% conversion of **4c**, products **5b** (46%) and **7** (21%) were isolated (see Scheme 2).

Further on we moved to the oxidation of imidazolin-2-one **4a** with HNO_3 (Scheme 3)[‡] using our experience[26] in the oxidation of 1-substituted 4,5-diarylimidazolin-2-ones to form 1-substituted 4,5-diaryl-5-hydroxy-3-imidazolin-2-ones. The target DHI **1a** was obtained in 95% yield being the mixture of (*meso*)-*cis*- and (*rac*)-*trans*-isomers *cis*-**1a** and *trans*-**1a** in a 2 : 1 ratio. To expand the scope of this method, the oxidation of other 1,3-dialkylimidazolin-2-ones **4b–i** and DHIs **1b–i** (yields 87–97%) was carried out. Whilst DHI **1b** was formed as a single *cis*-isomer, DHIs **1c**,**e–h** were isomer mixtures with a predominance of *cis*-products. When preparing DHIs **1d** and **1i**, a predominance of *trans*-isomers was observed. The ratio of *cis*- and *trans*-isomers was determined from the integral intensities of the signals for the aromatic CH groups by analogy with the known[22] data for DHIs *cis*-**1a** 6.84–7.05 [m, 10 H, CH(Ph)] and *trans*-**1a** 7.13–7.35 [m, 10 H, CH(Ph)]. It is of note that nitric acid of both 65 and 84% concentrations acted similarly.



3a–c **8a–d**

3a R = Me
3b R = Et
3c R = Pr

8a Ar = Ph
8b Ar = 4-MeOC$_6$H$_4$
8c Ar = 4-FC$_6$H$_4$
8d Ar = 4-MeC$_6$H$_4$

4a–i *cis*-**1a–i** (*meso*) *trans*-**1a–i** (*rac*)

4a, **1a** R = Me, Ar = Ph (ii, 95%, *cis*/*trans* = 2 : 1)
4b, **1b** R = Et, Ar = Ph (i, 53%; ii, 96%, *cis*/*trans* = 1 : 0)
4c, **1c** R = Et, Ar = 4-MeOC$_6$H$_4$ (i, 48%; ii, 97%, *cis*/*trans* = 3 : 1)
4d, **1d** R = Me, Ar = 4-MeOC$_6$H$_4$ (i, 67%; ii, 93%, *cis*/*trans* = 1 : 2.4)
4e, **1e** R = Pr, Ar = Ph (i, 54%; ii, 96%, *cis*/*trans* = 1.78 : 1)
4f, **1f** R = Pr, Ar = 4-MeOC$_6$H$_4$ (i, 50%; ii, 94%, *cis*/*trans* = 1.3 : 1)
4g, **1g** R = Me, Ar = 4-FC$_6$H$_4$ (i, 54%; ii, 96%, *cis*/*trans* = 25 : 1)
4h, **1h** R = Et, Ar = 4-FC$_6$H$_4$ (i, 51%; ii, 87%, *cis*/*trans* = 9 : 1)
4i, **1i** R = Et, Ar = 4-MeC$_6$H$_4$ (i, 57%; ii, 89%, *cis*/*trans* = 1 : 1.3)

Scheme 3 *Reagents and conditions*: i, $(CH_2OH)_2$, 170–180 °C, 2 h; ii, HNO_3 (65 or 84% aq.), MeCN, room temperature, 2 min.

The synthesis of imidazolin-2-ones **4a** and **4d** was carried out according to known procedures.[27] Previously undescribed imidazolin-2-ones **4b**,**c**,**e–i** were synthesized similarly by reacting the corresponding acyloins **8a–d** with ureas **3a–c** (1.5 equiv.) in ethylene glycol at 170–180 °C for 2 h with yields from 50 to 67%. Acyloins **8c**,**d** were obtained using known methods from 4-fluorobenzaldehyde and 4-methylbenzaldehyde, respectively.[28]

In summary, the oxidation of 1,3-dialkylimidazolin-2-ones with 65 or 84% HNO_3 was examined for the first time, which provided the effective synthesis of DHIs. The procedure is suitable for a broader scope of imidazolin-2-ones based on variety of acyloins and 1,3-dialkylureas.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2024.01.035.

[†] *Oxidation of 1,3-dialkyl-4,5-diaryl-4-imidazolin-2-ones* **4b**,**c** *with* $^1O_2$ *(general procedure).* A suspension of 1,3-dialkyl-4,5-diaryl-4-imidazolin-2-one (0.00379 mol) in DMSO (15 ml) in a weighting bottle (70 × 35 mm) was irradiated with UV light (254 nm, 6 W) at room temperature for 70 h. The lamp was located 2 cm above the weighting bottle. Then the resulting precipitate of 1,3-dialkyl-1*H*-phenanthro[9,10-*d*]imidazol-2(3*H*)-one **5a**,**b** was filtered off, washed with DMSO (1 ml) and dried. Water (50 ml) and $CHCl_3$ (40 ml) were added to the filtrate, the organic layer was separated and evaporated to dryness. The residue was separated by column chromatography ($CHCl_3$–MeCN, 5 : 1).

[‡] *Synthesis of 1,3-dialkyl-4,5-diaryl-4,5-dihydroxy-4-imidazolin-2-ones* **1a**–**i** *(general procedure).* Nitric acid (8 ml, 65% aq., or 5 ml, 84% aq.) was added dropwise to a suspension of the appropriate imidazolin-2-one **4a**–**i** (7 mmol) in MeCN (20 ml). The reaction was monitored visually by the dissolution of the solid reactant **1a**–**i** and by the change in color of the solution. The mixture was then extracted with $CHCl_3/H_2O$ (1 : 3), the $CHCl_3$ layer was evaporated, and the product was washed with Et_2O.

Synthesis of 1,3-dialkyl-4,5-diaryl-4-imidazolin-2-ones **4b**,**c**,**e–i** *(general procedure).* A mixture of appropriate 1,2-diaryl-2-hydroxyethanone **8** (0.05 mol) and urea **3** (0.125 mol) in ethylene glycol (20 ml) was heated at 170–180 °C for 2 h with stirring. After cooling to room temperature, the reaction mixture was extracted with $CHCl_3/H_2O$ (1 : 3, 100 ml) and washed with H_2O (3 × 100 ml). Then the $CHCl_3$ layer was evaporated. Products **4b**,**c**,**e–i** were isolated by column chromatography ($CHCl_3$–MeCN, 5 : 1).

References

1. S. Soma and Y. Morimoto, *Patent WO 2018066607A1*, 2018.
2. A. Hazarika and T. K. Maji, *Polym. Eng. Sci*., 2013, **53**, 1394.
3. X. Peng and Y. Liu, *Patent CN 115232528A*, 2022.
4. Y. Liu and X. Peng, *Patent CN 115181468A*, 2022.
5. S. Sakashita, K. Ueda, T. Horiguchi, M. Umemura and Y. Tsuge, *Patent JP 2022156870A*, 2022.
6. H. Zhang, A. Wang and L. Liang, *Patent CN 113372562A*, 2021.
7. T. Soubam, A. Gupta, S. Sharma and S. S. Jamari, *Mater. Today: Proc*., 2022, **68**, 756.
8. (*a*) J. A. Morris, J. E. Boehmer, A. J. Hennessy, T. R. Desson, S. E. Russell, C. J. Russell, B. Pickett, N. Kaloumenos and A. Balogh, *Patent WO 2016162265A1*, 2016; (*b*) M. Phadte, R. Sonawane, J. A. Morris, J. E. Boehmer, T. R. Desson, S. E. Russell, K. Ling, A. J. Hennessy, M. B. Hotson, A. Longstaff, C. J. Russell and J. Goodwin-Tindall, *Patent WO 2015052076A1*, 2015.
9. D. S. Mei and B. K. He, *Patent CN 113735845A*, 2021.
10. A. D. Shutalev, *Chem. Heterocycl. Compd*., 1993, **29**, 1421 (*Khim. Geterotsikl. Soedin*., 1993, 1645).
11. (*a*) E. Grillon, R. Gallo, M. Pierrot, J. Boileau and E. Wimmer, *Tetrahedron Lett*., 1988, **29**, 1015; (*b*) L. V. Saloutina, A. Ya. Zapevalov, P. A. Slepukhin, M. I. Kodess, V. I. Saloutin and O. N. Chupakhin, *Chem. Heterocycl. Compd*., 2014, **50**, 958 (*Khim. Geterotsikl. Soedin*., 2014, 1040); (*c*) H. D. Correia, R. S. Cicolani, R. F. Moral and G. J.-F. Demets, *Synthesis*, 2016, **48**, 210; (*d*) J. Svec, M. Dusek, K. Fejfarova, P. Stacko, P. Klán, A. E. Kaifer, W. Li, E. Hudeckova and V. Sindelar, *Chem. – Eur. J.*, 2011, **17**, 5605; (*e*) J. Rivollier, P. Thuéry and M.-P. Heck, *Org. Lett*., 2013, **15**, 480; (*f*) M. A. Yawer, V. Havel and V. Sindelar, *Angew. Chem., Int. Ed*., 2015, **54**, 276; (*g*) V. V. Baranov, T. N. Vol'khina, N. G. Kolotyrkina and A. N. Kravchenko, *Mendeleev Commun*., 2022, **32**, 537; (*h*) V. V. Baranov, A. A. Baganova, I. E. Chikunov, V. A. Karnoukhova and A. N. Kravchenko, *Tetrahedron Lett*., 2019, **60**, 1174.
12. (*a*) A. N. Kravchenko, V. V. Baranov and G. A. Gazieva, *Russ. Chem. Rev*., 2018, **87**, 89; (*b*) N. N. Makhova, L. I. Belen'kii, G. A. Gazieva, I. L. Dalinger, L. S. Konstantinova, V. V. Kuznetsov, A. N. Kravchenko, M. M. Krayushkin, O. A. Rakitin, A. M. Starosotnikov, L. L. Fershtat, S. A. Shevelev, V. Z. Shirinian and V. N. Yarovenko, *Russ. Chem. Rev*., 2020, **89**, 55.
13. (*a*) V. A. Eres'ko, L. V. Epishina, O. V. Lebedev, M. V. Povstyanoi, L. I. Khmel'nitskii and S. S. Novikov, *Bull. Acad. Sci. USSR, Div. Chem. Sci*., 1980, **29**, 1138 (*Izv. Akad. Nauk SSSR, Ser. Khim*., 1980, 1594); (*b*) V. V. Baranov, Yu. V. Nelyubina, A. N. Kravchenko, N. G. Kolotyrkina and K. A. Biriukova, *Tetrahedron Lett*., 2015, **56**, 6085; (*c*) V. V. Baranov, A. A. Galochkin, Yu. V. Nelyubina, A. N. Kravchenko and N. N. Makhova, *Synthesis*, 2020, **52**, 2563.
14. A. N. Terpigorev and S. B. Rudakova, *Russ. J. Org. Chem*., 1998, **34**, 1026 (*Zh. Org. Khim*., 1998, **34**, 1078).
15. V. V. Baranov, A. N. Kravchenko and Yu. V. Nelyubina, *Mendeleev Commun*., 2014, **24**, 105.
16. A. N. Izmest'ev, L. V. Anikina, I. E. Zanin, N. G. Kolotyrkina, E. S. Izmalkova, A. N. Kravchenko and G. A. Gazieva, *New J. Chem*., 2022, **46**, 11632.
17. (*a*) L. V. Saloutina, M. I. Kodess, I. N. Ganebnykh, P. A. Slepukhin, V. I. Saloutin and O. N. Chupakhin, *Russ. J. Org. Chem*., 2023, **59**, 623 (*Zh. Org. Khim*., 2023, **59**, 507); (*b*) A. A. Galochkin, V. V. Baranov, K. A. Hansford, L. I. M. Friberg, E. D. Strel'tzova, E. S. Lipatov, Yu. V. Nelyubina and A. N. Kravchenko, *ChemistrySelect*, 2023, **8**, e202300765.
18. L. V. Saloutina, A. Yu. Zapevalov, P. A. Slepukhin, M. I. Kodess, V. I. Saloutin and O. N. Chupakhin, *Russ. Chem. Bull*., 2016, **65**, 473.
19. (*a*) S. Nishino, H. Shima, T. Shimano and K. Yoshimura, *Patent WO 2008007763A1*, 2008; (*b*) F. Puccetti, S. Lukin, K. Užarević, E. Colacino, I. Halasz, C. Bolm and J. G. Hernández, *Chem. – Eur. J*., 2022, **28**, e202104409.
20. (*a*) S. Aryal, C. A. Hone, M. I. J. Polson and D. J. Foley, *Chem. Sci*., 2023, **14**, 7905; (*b*) R. A. Lamb, N. T. Lucas, G. Lessene and B. C. Hawkins, *J. Org. Chem*., 2018, **83**, 10120; (*c*) T. Fiala, K. Sleziakova, K. Marsalek, K. Salvadori and V. Sindelar, *J. Org. Chem*., 2018, **83**, 1903; (*d*) V. G. Shtamburg, V. V. Shtamburg, A. A. Anishchenko, S. V. Shishkina, A. V. Mazepa and I. S. Konovalova, *Eur. Chem. Bull*., 2019, **8**, 282; (*e*) H. Petersen, *Synthesis*, 1973, 243; (*f*) W. Dietz and R. Mayer, *J. Prakt. Chem*., 1968, **37**, 78; (*g*) G. Schwenker, H. Guo and S. Bernhart, *Arch. Pharm*., 1992, **325**, 779.
21. A. R. Butler and E. Leitch, *J. Chem. Soc., Perkin Trans. 2*, 1977, 1972.
22. A. N. Kravchenko, V. V. Baranov, Yu. V. Nelyubina, G. A. Gazieva and I. V. Svitan'ko, *Russ. Chem. Bull*., 2012, **61**, 64 (*Izv. Akad. Nauk, Ser. Khim*., 2012, 63).
23. V. D. Patul, V. D. Gharat and A. M. Salve, *Res. J. Chem. Environ*., 2021, **25**, 123.
24. A. N. Kravchenko, S. V. Vasilevskii, G. A. Gazieva, V. V. Baranov, V. A. Barachevsky, O. I. Kobeleva, O. V. Venidiktova and V. A. Karnoukhova, *Tetrahedron*, 2018, **74**, 2359.
25. H. Biltz and O. Behrens, *Ber*., 1910, **43**, 1984.
26. A. N. Kravchenko, M. M. Antonova, V. V. Baranov and Yu. V. Nelyubina, *Synlett*, 2015, **26**, 2521.
27. (*a*) Y. B. Kim, C. S. Kim and C. K. Lee, *J. Heterocycl. Chem*., 1994, **31**, 1653; (*b*) A. Ripka, G. Shapiro and R. Chesworth, *Patent WO 2009158393A1*, 2009.
28. T. Matsuyama, T. Yatabe, T. Yabe and K. Yamaguchi, *ACS Catal*., 2022, **12**, 13600.

Received: 8th November 2023; Com. 23/7298