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A simple synthesis of natural spinazarins and their analogues

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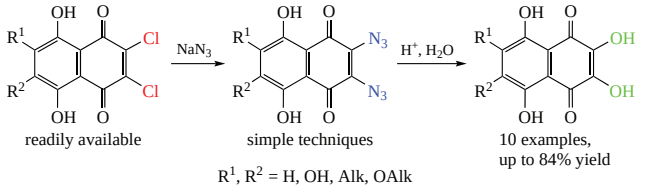
A short simple synthesis of spinazarins (2,3-dihydroxynaphthazarins or 2,3,5,8-tetrahydroxy-1,4-naphthoquinones) from available 2,3-dichloronaphthazarin derivatives involves replacement of chlorine atoms with azido groups followed by their acidic hydrolysis. The procedure can be used for the preparative synthesis of natural biologically active spinazarins and their analogues.



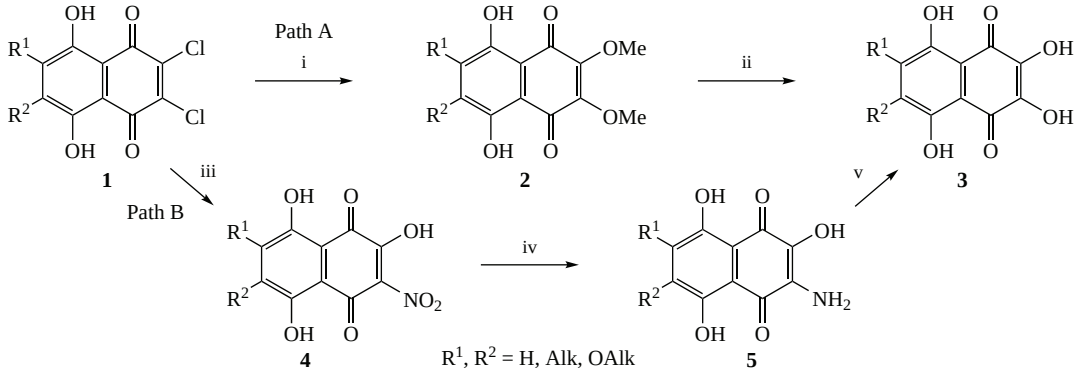
Keywords: 5,8-dihydroxy-1,4-naphthoquinone, naphthazarin, 2,3-dihydroxynaphthazarin, spinazarin, organic azides, hydrolysis, sea urchin pigments.

Against the background of thousands of 1,4-naphthoquinone derivatives presented in Thomson's multivolume monograph[1], 2,3-dihydroxynaphthazarins (2,3,5,8-tetrahydroxy-1,4-naphthoquinones, spinazarins) and their derivatives occupy an important place.Their first representatives were isolated more than one hundred years ago, but information on the isolation of new spinazarin derivatives[2–7] and their synthesis[8–11] is still documented. Some natural compounds of this series and their synthetic analogues are biologically active with antibacterial,[12] antiviral,[13,14] trypanocidal,[15] anticancer,[16–19] antimalarial,[20] antifungal,[21] and cardioprotective[22] properties or are active drugs.[23,24] Thus, the development of new effective syntheses of spinazarin derivatives remains urgent.

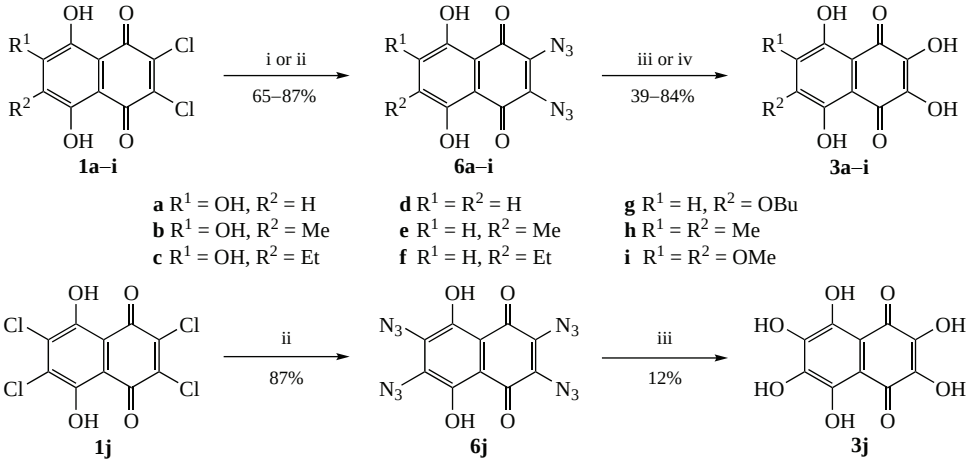
To date, approaches for the synthesis of spinazarin derivatives deal with the Diels–Alder reaction,[25] oxidation of functionally substituted α- and β-tetralones,[26] cycloacylation of hydroquinones with maleic anhydrides,[27–30] thermal rearrangement of 4-aryl-4-hydroxycyclobutenones[31] and some others.[32,33] All of them are not good for scaling due to multistage schemes, low overall yields or poor availability of initial substrates.

The cycloacylation of hydroquinones with dichloromaleic anhydride readily gives functionally substituted 2,3-dichloronaphthazarins **1** in high yields (Scheme 1).[27–30] However, the further replacement of chlorine atoms by methoxy groups with the aim of further conversion of intermediate 2,3-dimethoxynaphthazarins **2** into spinazarin derivatives required a huge excess of saturated sodium methoxide solution in methanol.[34] The problem was solved by the use of methanol activated by fluoride anion in the presence of alumina.[35,36] In many cases, the most appropriate reagent for the conversion of alkoxy naphthazarins into the corresponding hydroxy derivatives is aluminum chloride in nitrobenzene (Scheme 1, Path A).[36] An alternative sequential conversion of 2,3-dichloro-1,4-naphthoquinones **1** to 2-hydroxy-3-nitro- and further 3-amino-2-hydroxy-1,4-naphthoquinones[37] was later adapted for the synthesis of 2,3-dihydroxynaphthazarins **4** and **5**, respectively (Path B).[38–41] However, both methods gave low yields of β-OH derivatives.

This work describes a simple two-stage method for the preparation of spinazarins from the corresponding 2,3-dichloro



Scheme 1 *Reagents and conditions*: i, ROH, K(Cs)F, alumina, 90–100 °C, 6–12 h; ii, $AlCl_3$, $PhNO_2$; iii, $NaNO_2$, MeOH–acetone, reflux; iv, $Na_2S_2O_4$ or Na_2S; v, HCO_2H–H_2O–H_2SO_4, reflux.



Scheme 2 *Reagents and conditions*: i, NaN_3, DMSO, room temperature, 12 h; ii, NaN_3, MeOH, reflux, 6 h (for **1d**–**j**); iii, **6a**–**f**,**h**,**j** (2 mmol), AcOH–H_2O–H_2SO_4 (3 : 2.5 : 0.25, v / v, 160 ml), 120 °C, 1 h; iv, **6g**,**i** (2 mmol), HCO_2H–DMSO–H_2O–H_2SO_4 (8 : 2.7 : 1 : 0.1.7, v/v, 185 ml), 120 °C, 1 h.

Table 1 Optimization of the conditions for transformation **6a** → **3a**.[a]

Entry	Medium[b]	*t* / h	HPLC yield of **3a** (%)
1[c]	HCO_2H–DMSO (1:1)	4.5	1
2[d]	HCO_2H–DMSO–H_2O–H_2SO_4 (2.5 : 0.8 : 0.3 : 0.05)	0.5	79[e]
3	AcOH	1	3
4	AcOH–H_2O–H_2SO_4 (2.6 : 0.3 : 0.05)	1	79
5	AcOH–HCO_2H–H_2O–H_2SO_4 (2.6 : 0.1 : 0.3 : 0.05)	1	82
6	AcOH–HCO_2H (2.8 : 0.2)	1	7
7	AcOH–H_2O–CF_3CO_2H (1 : 1 : 1)	2	51
8	H_2O–CF_3CO_2H (2 : 1)	2	82
9	H_2O–CF_3CO_2H (1 : 1)	2	63[f]
10	H_2O–$MeSO_3H$ (1 : 1)	1	88
11	H_2O–H_2SO_4 (2.6 : 0.2)	1	62
12	AcOH–H_2O–H_2SO_4 (1.5 : 1.25 : 0.13)	1	92

[a] Initial concentration of **6a** 16.7 mM in 0.05 mmol scale runs, total volume of the media 3 ml. [b] Volume ratios of the components. [c] Method A described in ref. 40. [d] Method B described in ref. 40. [e] Recovery of **6a** 4%. [f] Recovery of **6a** 10%.

derivatives **1a**–**j** based on the replacement of chlorine atoms with azido groups followed by the acid-catalyzed conversion of diazides **6a**–**j** to dihydroxy naphthazarins **3a**–**j** (Scheme 2).[†] Most of the obtained azido derivatives, with the exception of **6d**, are new compounds. Their structure is confirmed by spectral (IR, NMR, HRMS) data. In the IR spectra of azido derivatives, the azido group appears as a highly intense band in the region of about 2110 cm^{-1}.

Chemistry of organic azides has been the subject of investigations because of their importance in the synthesis of amides, urea derivatives, carbamates, urethanes, and nitrogen-containing heterocyclic compounds.[42–44] Azido-1,4-benzo- and azido-1,4-naphthoquinones are easily prepared and can function as penultimate precursors to a large variety of other valuable compounds.[45] However, the properties of azido-substituted naphthazarins were less studied, *viz.*, only their cytotoxic activity[46] and conversion to amino derivatives have been described.[47]

Based on reported DMSO-mediated transformation of 3-amino-2-hydroxynaphthazarins to 2,3-dihydroxy-naphthazarins,[40] the known ease of azido group reduction to the amino one, and the assumption that 2,3-diaminonaphthazarins are likely intermediates of the reaction, we converted 2,3-diazidonaphthazarins into 2,3-dihydroxynaphthazarins. The conditions described[40] (Table 1, entries 1 and 2) were taken as the starting points for optimization. The presence of formic acid in the reaction mixture could explain the reduction of azido naphthazarins to amino derivatives, and the presence of DMSO could account for the conversion of 2,3-diamino derivatives to 2,3-dihydroxy derivatives (spinazarins), similar to that described.[40] However, further optimization of the conditions showed that the presence of water and a strong acid was sufficient for the successful conversion of the diazido derivatives to spinazarins (entries 8–10).

6,7-Diazido-2-hydroxynaphthazarin **6a** as a precursor of spinochrome D **3a**, one of the most demanded and difficult to obtain spinochromes, was used as the model compound to optimize the reaction conditions. A mixture acetic acid–water–sulfuric acid (see Table 1, entry 12) was chosen as optimal for conversion, since it provides sufficient solubility of the starting diazide **6a**, greater conversion to the desired product **3a** and less resinification of the reaction mixture. The long reaction time (entry 1) and the low solubility of the starting azide in aqueous sulfuric acid (entry 11) lead to a strong resinification of the reaction mixture. The absence of a strong acid in the reaction mixture (entries 1, 3, 6) results in a low yield of the desired product **3a**.

Optimized conditions were used to obtain a number of 2,3-dihydroxynaphthazarins **3**, among which several natural sea urchin pigments such as spinazarin **3d**, ethylspinazarin **3f**, echinochrome A **3b**, spinochromes D **3a** and E **3j** were present (see Scheme 2). However, the reaction of butoxy derivative **6g** in a mixture AcOH–H_2SO_4–H_2O is accompanied by hydrolysis of the alkoxy group and gives spinochrome D **3a** in 52% yield. In order to preserve alkoxy groups, described in ref. 40, mixture of formic and dilute sulfuric acids with the addition of DMSO was used for the conversion of alkoxy diazides **6g**,**i**. It should also be noted that the yield of final polyhydroxy naphthazarins **6a**–**j** depends on the solubility of the starting azido derivatives. Thus, the lowest yields and strong resinification were observed for less polar azido derivatives **3g**,**i**, and especially **3j**, which were almost insoluble in the solvent systems used.

The applicability of thus developed procedure for chlorinated derivatives containing β-hydroxy groups **6a**–**c** is an advantage over the previously described methods.[35–41] Most starting 2,3-dichloronaphthazarins **1** can be readily obtained by

[†] In each case the structures of naphthazarin (5,8-dihydroxy-1,4-naphthoquinone) derivatives are given only for one of all possible tautomers.

cycloacylation of 1,4-dimethoxy (or 1,4-dihydroxy) benzenes with commercially available dichloromaleic anhydride or by chlorination of naphthazarins in the HCl/MnO_2 system.[27–30] In turn, 2,3-diazidonaphthazarins **6** can be easily prepared from the corresponding 2,3-dichloro derivatives **1** in high yields. The reactions of sodium azide with 2,3-dichloronaphthazarins not containing β-OH groups can be carried out in methanol or acetone solution, while for substrates with β-OH groups DMSO or DMF should be employed.

In summary, a novel and concise approach to 2,3-dihydroxynaphthazarins has been developed. Many of these compounds are natural biologically active compounds that are difficult to obtain by other methods. The developed technique makes these compounds more accessible for a detailed study of the biological activity and use in the synthesis of other natural quinonoid compounds and their analogues.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2023.02.026.

References

1 R. H. Thomson, *Naturally Occurring Quinones*, 4th edn., Blackie Academic & Professional, London, 1997.
2 N. P. Mischenko, S. A. Fedoreyev, N. D. Pokhilo, V. Ph. Anufriev, V. A. Denisenko and V. P. Glazunov, *J. Nat. Prod*., 2005, **68**, 1390.
3 A. Ya. Yakubovskaya, N. D. Pokhilo, N. P. Mischenko and V. Ph. Anufriev, *Russ. Chem. Bull.*, 2007, **56**, 819 (*Izv. Akad. Nauk, Ser. Khim*., 2007, 788).
4 D. Y. Zhou, L. Qin, B.-W. Zhu, X.-D. Wang, H. Tan, J.-F. Yang, D.-M. Li, X.-P. Dong, H.-T. Wu, L.-M. Sun, X.-L. Li and Y. Murata, *Food Chem*., 2011, **129**, 1591.
5 N. P. Mischenko, E. A. Vasileva and S. A. Fedoreyev, *Tetrahedron Lett*., 2014, **55**, 5967.
6 A. N. Shikov, O. N. Pozharitskaya, A. S. Krishtopina and V. G. Makarov, *Phytochem. Rev*., 2018, **17**, 509.
7 E. A. Vasileva, N. P. Mishchenko and S. A. Fedoreyev, *Chem. Biodiversity*, 2017, **14**, e1700182.
8 N. D. Pokhilo, A. Ya. Yakubovskaya, V. A. Denisenko and V. Ph. Anufriev, *Tetrahedron Lett*., 2006, **47**, 1385.
9 T. Yu. Kochergina and V. Ph. Anufriev, *Chem. Nat. Compd*., 2011, **47**, 10 (*Khim. Prir. Soedin*., 2011, 12).
10 G. I. Melman, K. L. Borisova, N. D. Pokhilo, V. V. Makhankov and V. Ph. Anufriev, *Tetrahedron Lett*., 2016, **57**, 736.
11 D. N. Pelageev and V. Ph. Anufriev, *Synthesis*, 2016, **48**, 761.
12 J. M. Sánchez-Calvo, G. R. Barbero, G. Guerrera-Vásquez, A. G. Durán, M. Macías, M. A. Rodríguez-Iglesias, J. M. G. Molinillo and F. A. Macías, *Med. Chem. Res*., 2016, **25**, 1274.
13 S. G. Polonik, N. V. Krylova, G. G. Kompanets, O. V. Iunikhina and Yu. E. Sabutski, *Nat. Prod. Commun*., 2019, DOI: 10.1177/1934578X19860672.
14 S. A. Fedoreyev, N. V. Krylova, N. P. Mishchenko, E. A. Vasileva, E. A. Pislyagin, O. V. Iunikhina, V. F. Lavrov, O. A. Svitich, L. K. Ebralidze and G. N. Leonova, *Mar. Drugs*, 2018, **16**, 509.
15 L. Salmon-Chemin, E. Buisine, V. Yardley, S. Kohler, M. A. Debreu, V. Landry, C. Sergheraert, S. L. Croft, L. R. Krauth-Siegel and E. Davioud-Charvet, *J. Med. Chem.*, 2001, **44**, 548.
16 K. W. Wellington, *RSC Adv*., 2015, **5**, 20309.
17 D. L. Aminin and S. G. Polonik, *Chem. Pharm. Bull*., 2020, **68**, 46.
18 S. A. Dyshlovoy, D. N. Pelageev, J. Hauschild, Yu. E. Sabutskii, E. A. Khmelevskaya, C. Krisp, M. Kaune, S. Venz, K. L. Borisova, T. Busenbender, V. A. Denisenko, H. Schlüter, C. Bokemeyer, M. Graefen, S. G. Polonik, V. Ph. Anufriev and G. von Amsberg, *Mar. Drugs*, 2020, **18**, 251.
19 S. A. Dyshlovoy, D. N. Pelageev, L. S. Jakob, K. L. Borisova, J. Hauschild, T. Busenbender, M. Kaune, E. A. Khmelevskaya, M. Graefen, C. Bokemeyer, V. Ph. Anufriev and G. von Amsberg, *Pharmaceuticals*, 2021, **14**, 949.
20 S. El Hage, M. Ane, J.-L. Stigliani, M. Marjorie, H. Vial, G. Baziard-Mouysset and M. Payard, *Eur. J. Med. Chem.*, 2009, **44**, 4778.
21 D. O. Futuro, P. G. Ferreira, C. D. Nicoletti, L. P. Borba-Santos, F. C. Da Silva, S. Rozental and V. F. Ferreira, *Annals of the Brazilian Academy of Sciences*, 2018, **90** (1 Suppl. 2), 1187.
22 Ch. Sh. Yoon, H. K. Kim, N. P. Mishchenko, E. A. Vasileva, S. A. Fedoreyev, V. A. Stonik and J. Han, *Mar. Drugs*, 2019, **17**, 2.
23 G. B. Elyakov, O. B. Maximov, N. P. Mischenko, E. A. Koltsova, S. A. Fedoreev, L. I. Glebko, N. P. Krasovskaya and A. A. Artjukov, *US Patent 6384084*, 2002.
24 G. B. Elyakov, O. B. Maximov, N. P. Mischenko, E. A. Koltsova, S. A. Fedoreev, L. I. Glebko, N. P. Krasovskaya and A. A. Artjukov, *US Patent 6410601*, 2002.
25 F. Farina, M. Lora-Tamayo and C. Suarez, *An. R. Soc. Esp. Fis. Quim., Ser. B*, 1963, **59**, 167.
26 H. A. Anderson, J. Smith and R. H. Thomson, *J. Chem. Soc*., 1965, 2141.
27 I. Singh, R. E. Moore, C. W. J. Chang, R. T. Ogata and P. J. Scheuer, *Tetrahedron*, 1968, **24**, 2969.
28 R. Huot and P. Brassard, *Can. J. Chem.*, 1974, **52**, 838.
29 V. Ph. Anufriev, S. G. Polonik, N. D. Pokhilo and N. N. Balanyova, *Russ. Chem. Bull*., 2003, **52**, 2247 (*Izv. Akad. Nauk, Ser. Khim.*, 2003, 2128).
30 V. L. Novikov, N. N. Balaneva, O. P. Shestak, V. Ph. Anufriev and V. P. Glazunov, *Russ. Chem. Bull*., 2016, **65**, 993.
31 H. W. Moore and S. T. Perri, *J. Org. Chem*., 1988, **53**, 996.
32 F. Weygand, K. Vogelbach and K. Zimmermann, *Chem. Ber*., 1947, **80**, 391.
33 F. Weygand, H. Weber and E. Maekawa, *Chem. Ber*., 1957, **90**, 1879.
34 I. Singh, R. E. Moore, C. W. J. Chang and P. J. Scheuer, *J. Am. Chem. Soc*., 1965, **87**, 4023.
35 V. Ph. Anufriev and V. L. Novikov, *Tetrahedron Lett.*, 1995, **36**, 2515.
36 V. Ph. Anufriev, V. L. Novikov, O. B. Maximov, G. B. Elyakov, D. O. Levitsky, A. V. Lebedev, S. M. Sadretdinov, A. V. Shvilkin, N. I. Afonskaya, M. Ya. Ruda and N. M. Cherpachenko, *Bioorg. Med. Chem. Lett*., 1998, **8**, 587.
37 H. Ulrich and R. Richter, in *Methoden der Organischen Chemie*, eds. I. Houben and T. Weyl, Thieme, Stuttgart, 1977, vol. 7/3a, pp. 404–412.
38 S. G. Polonik, N. S. Polonik, V. A. Denisenko, O. P. Moiseenko and V. Ph. Anufriev, *Russ. J. Org. Chem*., 2009, **45**, 1410 (*Zh. Org. Khim.*, 2009, **45**, 1423).
39 N. S. Polonik, S. G. Polonik, V. A. Denisenko and O. P. Moiseenko, *Synthesis*, 2011, 3350.
40 N. S. Polonik and S. G. Polonik, *Tetrahedron Lett*., 2016, **57**, 3303.
41 Yu. E. Sabutskii, V. A. Denisenko and S. G. Polonik, *Synthesis*, 2018, **50**, 3738.
42 S. Brase, C. Gil, K. Knepper and V. Zimmermann, *Angew. Chem., Int. Ed*., 2005, **44**, 5188.
43 H. Tanimoto and K. Kakiuchi, *Nat. Prod. Commun*., 2013, **8**, 1021.
44 S. V. Chapyshev, *Molecules*, 2015, **20**, 19142.
45 H. W. Moore, *Chem. Soc. Rev*., 1973, **2**, 415.
46 N. D. Pokhilo, M. I. Kiseleva and V. F. Anufriev, *Pharm. Chem. J*., 2011, **45**, 522 [*Khim.-Farm. Zh*., 2011, **45** (9), 8].
47 N. D. Pokhilo, M. I. Shuvalova, M. V. Lebedko, G. I. Sopelnyak, A. Ya. Yakubovskaya, N. P. Mischenko, S. A. Fedoreyev and V. Ph. Anufriev, *J. Nat. Prod*., 2006, **69**, 1125.

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