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Regiospecificity in the reaction of 2,3-dichloronaphthazarins with azide anions. Synthesis of echinamine A—a metabolite produced by the sea urchin *Scaphechinus mirabilis*

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Abstract—It was found that 6-hydroxy- and 6-alkoxy-2,3-dichloronaphthazarins react smoothly with sodium azide in methanol to produce the corresponding 2-azido derivatives as single regioisomers. We have explored the utility of this reaction for the synthesis of echinamine A (3-amino-7-ethyl-2,5,6,8-tetrahydroxy-1,4-naphthoquinone)—the first marine aminated hydroxynaphthazarin, a metabolite of the sea urchin *Scaphechinus mirabilis* (Agassiz).

Nucleophilic substitution of haloids in chlorinated naphthazarins (5,8-dihydroxy-1,4-naphthoquinones) is an important method for the modification of their structures.[1] Some of the compounds produced in this way possess biological activity,[1b,2] or are known as drugs.[3] However, the reported methods in many cases have the limitation of low regioselectivity.[2d,4] Thus, the substitution of a chlorine atom by a methoxy group in 2,3-dichloro-6-hydroxynaphthazarin **1** affords products **2** and **3** in a 2:1 ratio (Fig. 1).[5]

We have found that substitution of a chlorine by an azido group in 6-hydroxy- and 6-alkoxy-2,3-dichloronaphthazarins by the action of NaN_3 in MeOH is directed by hydroxy- and alkoxy groups to position 2 only. Thus, the above-mentioned substrate **1** reacted smoothly with sodium azide to give 2-azido derivative **4**. Compound **4** was easily converted into the corresponding methoxy derivative **3** by the action of MeOH in the presence of K_2CO_3.

Chlorinated 7-ethyl-6-hydroxy- **5** and 7-ethyl-6-methoxynaphthazarin **6** in turn reacted with NaN_3 in MeOH to provide the corresponding monoazides **7** and **8** in excellent yields, and remarkably, as single regioisomers. On the contrary, dichloroethylnaphthazarin **9** under these conditions gave a mixture of monoazides **10** and **11** (Fig. 1). The position of the azido groups in

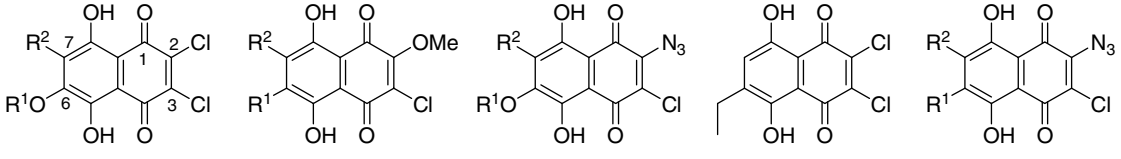

Figure 1.

Keywords: 2,3-Dichloronaphthazarins; Azido group; Regiospecificity of substitution; Echinamine A; 3-Amino-7-ethyl-2,5,6,8-tetrahydroxy-1,4-naphthoquinone; Sea urchin, *Scaphechinus mirabilis* (Agassiz).
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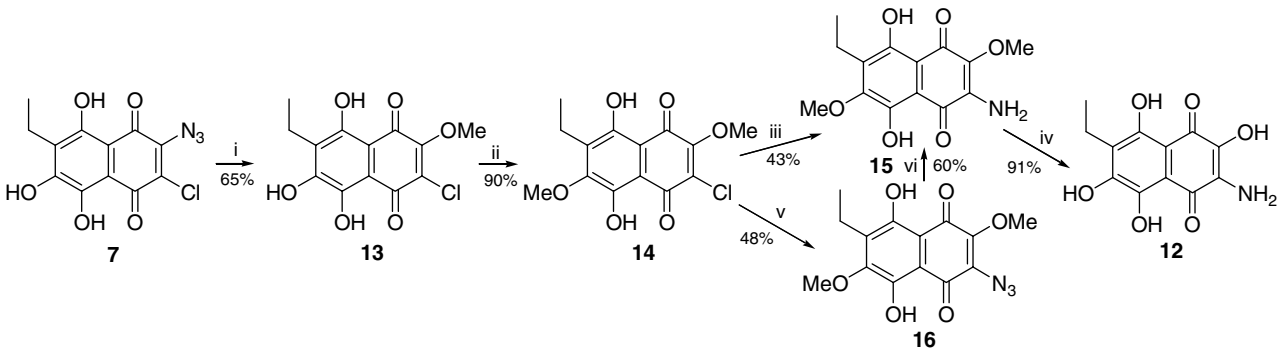
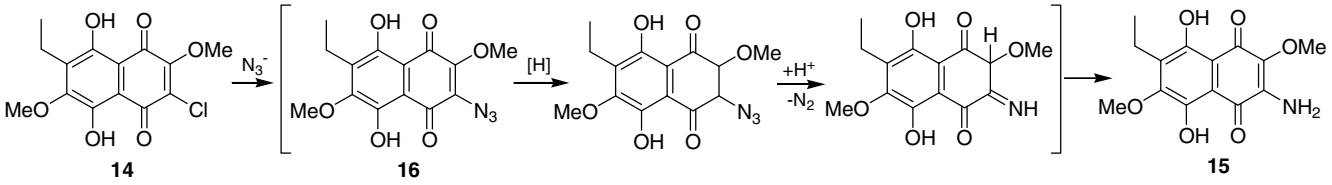


Scheme 1. Reagents and conditions: (i) K_2CO_3, MeOH, reflux, 2 h; (ii) CH_2N_2, Et_2O, rt; (iii) NaN_3, DMSO, 50 °C, 3 h; (iv) HBr–HOAc, reflux, 1 h; (v) NaN_3, MeOH, 50 °C, 2 h; (vi) DMSO, 50 °C, H^+.



Scheme 2.

compounds **4**, **7**, **8**, **10**, and **11** were unequivocally established by analysis of their NMR spectra and all assignments are supported by HMBC experiments.

These observations were used as the basis for the synthesis of echinamine A (3-amino-7-ethyl-2,5,6,8-tetrahydroxy-1,4-naphthoquinone, **12**), the first marine aminated hydroxynaphthazarin, produced by the sea urchin *S. mirabilis*[2d] (Scheme 1).[6]

As noted above, dichlorohydroxyethylnaphthazarin **5**[7] reacted with NaN_3 in MeOH to provide azido derivative **7** as a single regioisomer. This was converted to methoxy derivative **13**, then O-methylation gave substituted dimethoxynaphthazarin **14**. This compound reacted with an excess of NaN_3 in DMSO to give amino derivative **15**. Product **15**, probably, is the result of reduction of the corresponding azido-1,4-naphthoquinone **16** with HN_3 produced during treatment of the reaction mixture with water (Scheme 2). This reaction mechanism has previously been discussed in detail.[8] Azido-1,4-naphthoquinone **16** was isolated when the same reaction was conducted in MeOH. In DMSO azido derivative **16** was also converted into **15** (Scheme 1).

Finally, demethylation of dimethyl ether **15** gave aminohydroxynaphthazarin **12** in excellent yield. Synthetic compound **12** was identical in all respects with echinamine A isolated from the sea urchin *S. mirabilis*.[2d]

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6. Selected analytical data for some key compounds: Compound **7**: red solid; mp 120–124 °C; IR ($CHCl_3$) ν_{max}: 2128, 1603, 1560, 1421, 1318, 1279, 1143, 1091 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.15 (t, $J = 7.5$ Hz, 3H), 2.64 (q, $J = 7.5$ Hz, 2H), 7.28 (s, 1H), 12.26 (s, 1H), 13.61 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 182.5, 173.5, 160.4, 158.3,

153.7, 139.9, 126.5, 120.4, 107.7, 106.9, 16.3, 12.5; EIMS: m/z (%) = 309/311 (M^+, 55), 308/310 (18), 302/304 (13), 281/283 (100), 280/282 (61), 268 (13), 266 (19), 247 (22) 246 (94). Anal. Calcd for $C_{12}H_8ClN_3O_5$: C, 46.54; H, 2.60; N, 13.57%. Found: C, 46.57; H, 2.67; N, 13.55%. Compound **13**: red solid; mp 129–134 °C; IR ($CHCl_3$) ν_{max}: 3607, 3520, 3414, 1624, 1562, 1462, 1409, 1330, 1304, 1278 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 1.15 (t, $J = 7.5$ Hz, 3H), 2.62 (q, $J = 7.5$ Hz, 2H), 4.20 (s, 3H), 7.36 (br s, 1H), 12.22 (s, 1H), 13.47 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 186.4, 178.3, 157.5, 155.8, 154.8, 153.6, 126.7, 122.7, 109.5, 106.3, 61.8, 16.3, 12.5; EIMS: m/z (%) = 299/301 (M^++1, 13), 298/300 (M^+, 98), 284/286 (39), 283/285 (100), 280/282 (60), 270/272 (18), 293 (11), 256 (9); Anal. Calcd for $C_{13}H_{11}ClO_6$: C, 52.28; H, 3.71%. Found: C, 52.25; H, 3.80%. Compound **14**: red solid; mp 137–139 °C; ^1H NMR (500 MHz, $CDCl_3$) δ: 1.15 (t, $J = 7.5$ Hz, 3H), 2.69 (q, $J = 7.5$ Hz, 2H), 4.12, 4.25 (each s, 3H), 13.09 (s, 1H), 13.14 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 172.5, 170.6, 168.4, 166.2, 156.6, 156.2, 137.0, 126.0, 108.3, 108.5, 61.9, 61.6, 17.0, 13.4; EIMS: m/z (%) = 312/314 (M^+, 100), 311/313 (92), 297/299 (12), 296/298 (25), 294 (10), 293 (11), 256 (9); Anal. Calcd for $C_{14}H_{13}ClO_6$: C, 53.84; H, 4.20%. Found: C, 53.79; H, 4.30%. Compound **15**: yellow brown needles; mp 300 °C (dec.); IR ($CHCl_3$) ν_{max}: 3514, 3398, 1684, 1641, 1616, 1593, 1556 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.17 (t, $J = 7.5$ Hz, 3H), 2.74 (q, $J = 7.5$ Hz, 2H), 4.00, 4.01 (each s, 3H), 5.06 (br s, 2H), 12.52 (s, 1H), 13.48 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 182.7, 180.9, 158.4, 153.7, 152.8, 139.7, 138.2, 137.1, 107.4, 105.4, 61.3, 60.5, 17.4, 13.7; EIMS: m/z (%) = 293 (M^+, 100), 292 (30), 278 (76), 263 (22), 250 (31), 248 (37), 235 (27), 221 (26); Anal. Calcd for $C_{14}H_{15}NO_6$: C, 57.32; H, 5.16; N, 4.78%. Found: C, 57.25; H, 5.25; N, 4.90%.

7. The necessary starting substrate **5** was obtained according to the procedure described by Anufriev, V. Ph.; Polonik, S. G.; Pokhilo, N. D.; Balanyova, N. N. *Russ. Chem. Bull. Int. Ed.* **2003**, *52*, 2247–2250.
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