Use of Nitrile Oxides in Synthesis. A Novel Synthesis of Chalcones, Flavanones, Flavones and Isoflavones

Ib Thomsen and Kurt B. G. Torssell

Department of Organic Chemistry, Chemical Institute, University of Aarhus, DK-8000 Århus C, Denmark

Thomsen, I. and Torssell, K. B. G., 1988. Use of Nitrile Oxides in Synthesis. A Novel Synthesis of Chalcones, Flavanones, Flavones, and Isoflavones. – Acta Chem. Scand., Ser. B 42: 303–308.

Novel methodology is developed for a three-step synthesis of chalcones, flavanones, flavones and isoflavones. 1. Salicylaldoxime is chlorinated to the corresponding hydroxamoyl chloride in the presence of pyridine, and cycloadded to styrene and phenylacetylene. 2. The isoxazole derivatives formed are reductively cleaved over Raney-Ni to β-hydroxyketones or 1,3 diketones. 3. Acid-catalyzed cyclization gives the flavonoids. Use of ω-methoxy- or ω-dialkylamino-substituted styrenes (enamines) leads regioselectively to 4-aryl-substituted isoxazoles and the derived isoflavones.

As part of our current investigations of the use of nitrile oxides and silyl nitronates, we present a novel synthesis of flavonoids. In the preceding papers we described the application of these reagents in the synthesis of deoxysugars[1] and biheteroaromatics,[2] and our earlier papers document their value as versatile reagents in basic organic synthesis. The development in the field is reviewed in a monograph.[3]

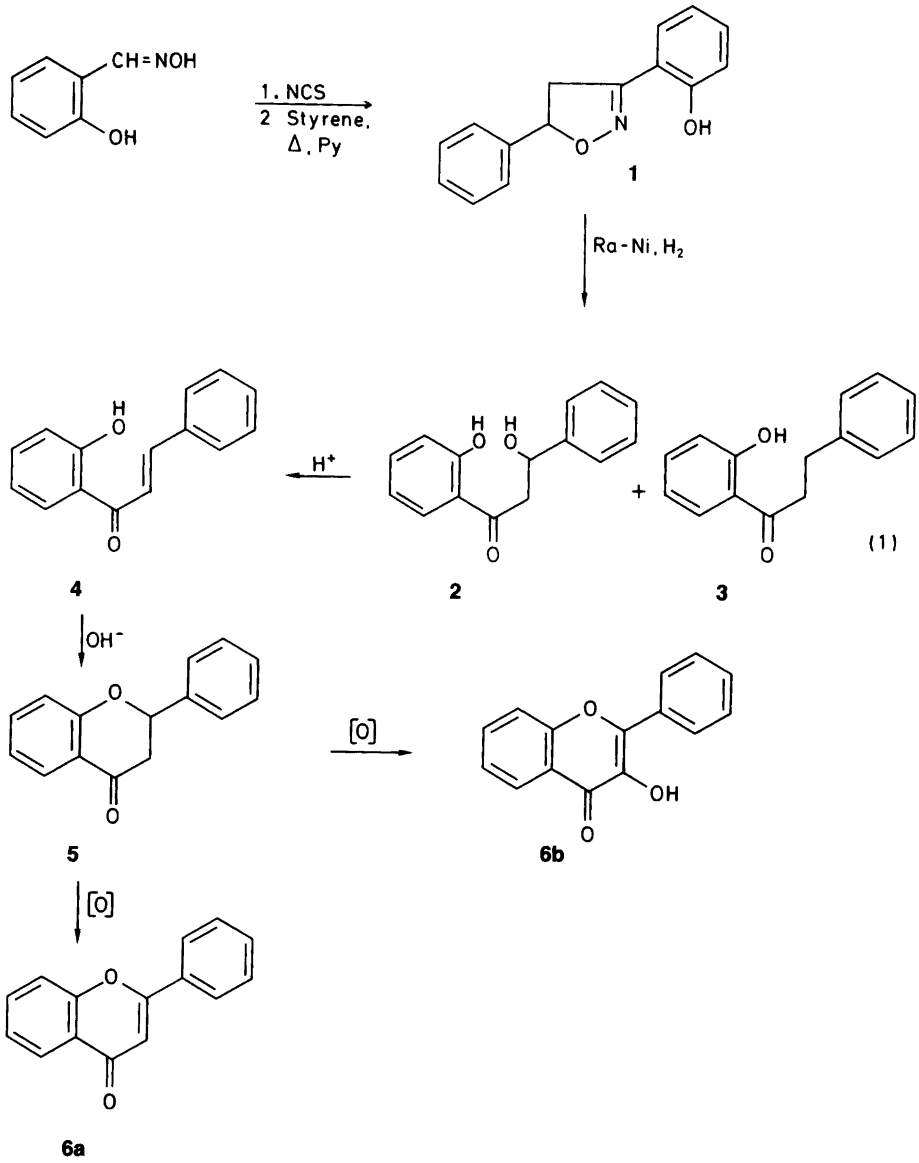
It has been shown that *N*-chlorosuccinimide (NCS) in chloroform selectively chlorinates aldoximes to hydroxamic acid chlorides in the presence of several other sensitive functions.[4] Salicylaldoxime gives the corresponding hydroxamic acid chloride without nuclear chlorination, and heating under reflux in chloroform in the presence of pyridine generates the nitrile oxide, which is trapped by olefins and acetylenes. Styrene gives 3-(2-hydroxyphenyl)-5-phenylisoxazoline (**1**). Catalytic reduction over Raney-Ni followed by elimination of water gives the chalcone **4** and subsequently the flavanone **5** [eqn. (1)]. The flavanone can be oxidized to flavone **6a** or flavonol **6b** by classical procedures.[§] By analogy, phenylacetylene gives the isoxazole **7**, which on reduction and acid-catalyzed cyclization forms the flavone **6a** [eqn. (2)].

7 can also be prepared by cycloaddition of the enamine of morpholine and acetophenone (**15**) to salicylhydroxamoyl chloride in the presence of base, followed by acid-catalyzed elimination of morpholine. This regioselective mode of cycloaddition has been noted earlier.[6a] Thus, acetylenes as well as methyl phenyl ketones can serve as starting material, which widens the scope of the reaction [eqn. (3)].

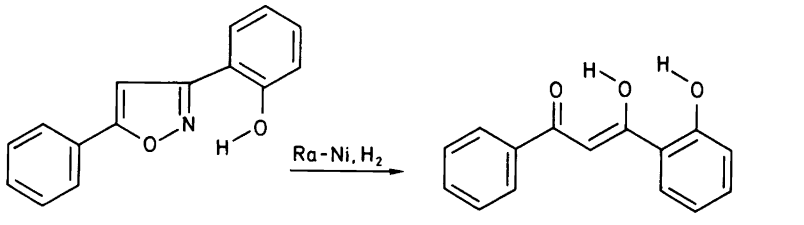
The di- and trihydroxylated benzaldoximes **9–11** undergo rapid nuclear halogenation with NCS and NBS and thus cannot be used without protection. The synthesis of some hydroxylated, naturally occurring flavones will be the subject of a separate paper.

Styrene and phenylacetylene thus react regioselectively to give 5-substituted isoxazoles leading to flavone derivatives as shown in eqn. (1). The synthesis of isoflavones requires access to 4-phenyl-substituted isoxazoles. This can be accomplished by using ω-oxy-substituted styrenes **12**, **13** or the enamine **14**, prepared from phenylacetaldehyde, as dipolarophiles [eqn. (4)]. The oxy and nitrogen functions are regioselectively directed to the 5-position, and they can be eliminated by treatment with acid.[6b,c] The enamine **14** gives the best yields of **17**, viz. ca. 50 %; **12** gives ca. 10 %, and **13** gives only traces of **17**. The reduction and cyclization of **17** to the isoflavone

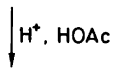
[§] See, e.g., Ref. 5.



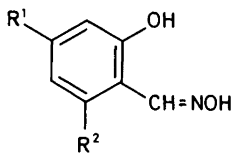
19 turned out not to be as straightforward as was anticipated. Ra-Ni-catalyzed reduction in methanol leads to some overreduction, and from the reaction mixture only the isoflavanone **18** was isolated, in a yield of ca. 10–15 %. This indicates that the N–O bond is reductively cleaved, the imino group formed is hydrolyzed, and that cyclization occurs to give **19**, this isoflavone being, however, further reduced to **18**. **19** was not observed with certainty in the crude product. In order to prevent the spontaneous cyclization, **17** was first acetylated with acetyl chloride and triethylamine, and then subjected to reduction and acid-catalyzed cyclization. This procedure gives the isoflavone **19** in a satisfactory yield. Thus, new general procedures for the synthesis of various flavonoids are now available.



7 8 (2)



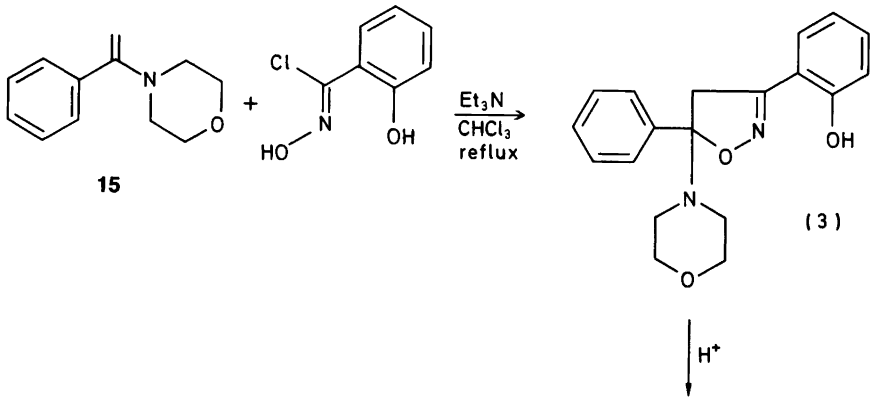
6a



9 $R^1 = R^2 = OCH_3$

10 $R^1 = R^2 = OH$

11 $R^1 = OH$, $R^2 = H$

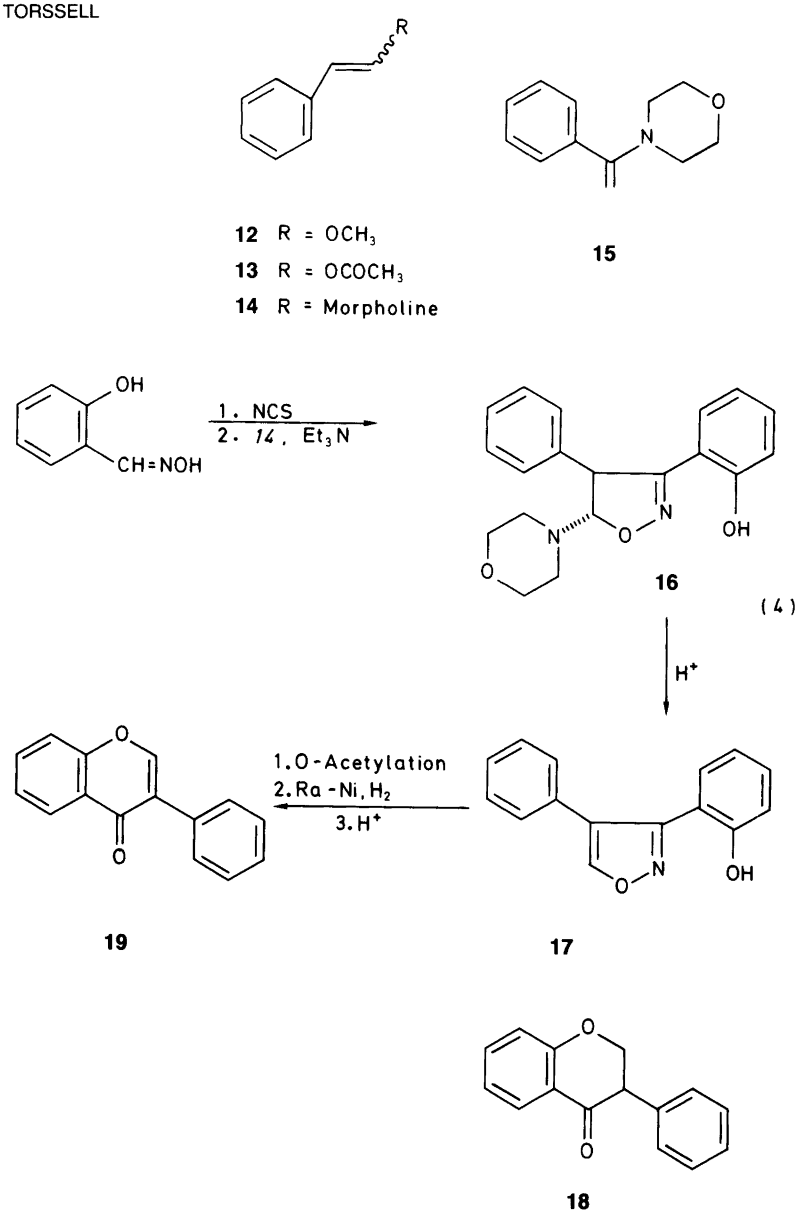


15 (3) 7

Experimental

3-(2-Hydroxyphenyl)-5-phenylisoxazoline (**1**). Salicylaldoxime **1** (2.07 g), styrene (2.10 g, 30 % excess), pyridine (1.20 g) and *N*-chlorosuccinimide (2.00 g) are heated under reflux in chloroform (30 ml) for 2 h. Washing with water, drying of the organic phase with $MgSO_4$, evaporation and column chromatography of the residue (SiO_2, CH_2Cl_2) give **1** (2.03 g, 54 %) as a light yellow oil. ^1H NMR ($CDCl_3$): δ 3.40 (1H, dd, *J* 16 and 8 Hz), 3.74 (1H, dd, *J* 16 and 10 Hz), 5.54 (1H, dd, *J* 10 and 8 Hz), 6.6–7.3 (9H, m), 9.8 (1H, s).

*3-Hydroxy-1-*o*-hydroxyphenyl-3-phenylpropan-1-one* (**2**) and *1-*o*-hydroxyphenyl-3-phenylpropan-1-one* (**3**) are obtained in 38 % yield and



14 % yield, respectively, by catalytic reduction over Raney-Ni in the presence of boric acid in methanol/water (5:1) as solvent. They are separated by preparative TLC (SiO_2; $CHCl_3$, 2 % CH_3OH). ^1H NMR ($CDCl_3$): **2**: oil, δ 3.3 (2H, m), 5.25 (1H, dd, *J* 6 and 7 Hz), 6.4–7.7 (9H, m); **3**: oil, δ 3.15 (4H, m), 6.4–7.8 (9H, m). MS: 226 (M^+).

The chalcone (**4**) is formed quantitatively by heating **2** under reflux for $^1/_2$ h in chloroform containing catalytic amounts of *p*-TsOH; m.p. 89 °C from diethyl ether (lit.[8] 88–89 °C). It is cyclized to the flavanone **5** according to Lövenbein's method;[9] m.p. 74 °C (lit.[8] 76 °C).

3-(2-Hydroxyphenyl)-5-phenylisoxazole (**7**) is prepared as described for **1** from phenylacetylene (100 % excess) and salicylaldoxime in a yield of 44 %; m.p. 115 °C from diethyl ether. ^{1}H NMR ($CDCl_3$): δ 6.73 (1H, s), 6.6–7.8 (9H, m), 9.40 (1H, s).

The isoxazole **7** is prepared by reacting the chlorinated salicylaldoxime with **15**. Heating the mixture under reflux with triethylamine in chloroform for 0.5 h and usual work-up give 43 % of **7**.

o-*Hydroxydibenzoylmethane* (**8**), enol form, is obtained in a yield of 64 % by catalytic reduction of **7** over Raney-Ni in methanol as solvent; m.p. 120 °C from chloroform (lit.[7] 120 °C).

8 is cyclized to flavone **6a** in practically quantitative yield by heating under reflux in acetic acid containing hydrogen chloride; m.p. 98 °C from cyclohexane (lit.[7] 99–100 °C).

2,4,6-Trihydroxybenzaldoxime (**10**) was prepared by reaction of hydroxylamine hydrochloride (0.35 g) with 2,4,6-trihydroxybenzaldehyde (0.80 g) in aqueous methanol (5 ml, 1:1) at room temperature for 16 h under nitrogen. Water is added and the solution is extracted five times with ether. The combined ether phase is dried over magnesium sulfate and evaporated, yielding 0.88 g of the oxime **10**; m.p. 197 °C (decomp., lit.[13] 195 °C). The oximes **9** and **11** were prepared similarly.

12 is commercially available; **13**, **14**, and **15** are prepared according to literature procedures.[10–12]

3-(2-Hydroxyphenyl)-4-phenylisoxazole (**17**). Salicylaldoxime (1.12 g) is chlorinated with NCS (1.36 g, 25 % excess) plus 2 drops of pyridine in chloroform under reflux (10 ml) for 20 min. The enamine **14** (1.56 g) is added at room temperature and then triethylamine dropwise (0.88 g, dissolved in 10 ml of chloroform). The mixture is heated under reflux for 1 h and evaporated. The residue is heated under reflux with hydrochloric acid (2 ml conc. in 5 ml of ethanol) for 1 h. Evaporation, followed by partition of the products between chloroform and water gives crude **17** which is purified by prep. TLC (SiO_2, CH_2Cl_2). 1.04 g (54 %) of pure **17** is obtained as a viscous light yellow oil. ^{1}H NMR ($CDCl_3$): δ 6.4–7.5 (9H, m), 8.32 (1H, s), 9.3 (1H, br.s).

The intermediate isoxazoline **16** can be isolated as a viscous oil in a yield of 69 % from the chloroform solution after reflux by washing it with water, drying the chloroform phase over magnesium sulfate, evaporating the solvent and purifying the residue by prep. TLC (SiO_2, $CHCl_3$, 1 % CH_3OH). ^{1}H NMR ($CDCl_3$): δ 2.6 (4H, m), 3.65 (4H, m), 4.48 (1H, d, *J* 3 Hz), 5.05 (1H, d, *J* 3 Hz), 6.5–7.5 (9H, m), 10.0 (1H, br.s). Catalytic reduction of **17** over Ra–Ni in methanol gives a crude product from which **18** can be isolated by prep. TLC (SiO_2, $CHCl_3$) in a yield of ca. 10–15 %. The reduction is stopped after the absorption of 1.1 equiv. of H_2. ^{1}H NMR ($CDCl_3$): δ 3.90 (1H, t, *J* 7 Hz), 4.60 (2H, d, *J* 7 Hz), 6.7–7.5 (8H, m), 7.87 (1H, dt, *J* 8 and 2 Hz). MS: M^+ 224.

The O-*acetyl derivate of* **17** is obtained by acetylation of **17** with acetyl chloride and triethylamine in chloroform at 20 °C. Washing with water and evaporation of the solvent gives the acetate in 93 % yield; m.p. 119–121 °C (from methanol). ^{1}H NMR ($CDCl_3$): δ 1.95 (3H, s), 7.0–7.6 (8H), 8.53 (1H, s).

The isoflavone (**19**). The acetate of **17** is quantitatively reduced with Ra–Ni/H_2 in aqueous methanol (15 % water). The solution is filtered and evaporated to dryness, and the product purified by chromatography on silica (CH_2Cl_2, 9 % CH_3OH). 0.20 g of the product is heated under reflux for $^1/_2$ h in 1 ml of ethanol containing one drop of conc. hydrochloric acid. Evaporation and purification by prep. TLC (SiO_2, $CHCl_3$, 10 % CH_3OH) give **19**; m.p. 133–135 °C from hexane (lit.[14] 131 °C and lit.[15] 148 °C). ^{1}H NMR ($CDCl_3$): δ 7.0–7.8 (8H, m), 7.98 (1H, s), 8.28 (1H, dd, *J* 8 and 2 Hz). MS: M^+ 222. The yield is 69 %.

References

1. Torssell, K. B. G., Hazell, A. C. and Hazell, R. G. *Tetrahedron 41* (1985) 5569.
2. Ghabrial, S. S., Thomsen, I. and Torssell, K. B. G. *Acta Chem. Scand., Ser. B 41* (1987) 426.
3. Torssell, K. B. G. *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis. Novel Strategies in Synthesis*, Verlag Chemie, New York 1988.
4. Larsen, K. E. and Torssell, K. B. G. *Tetrahedron 40* (1984) 2985.
5. Seshadri, T. R. In: Geissman, T. A., Ed., *The*

Chemistry of Flavonoid Compounds, Pergamon, Oxford 1962, p. 156.
6. (a) Bianchetti, G., Pocar, D., Dalla Croce, P. and Vigevani, A. *Chem. Ber. 98* (1965) 2715; (b) Bianchetti, G., Pocar, D. and Dalla Croce, P. *Gazz. Chim. Ital. 93* (1963) 1714; *Ibid.* 1726; (c) Adachi, I. and Kano, H. *Chem. Pharm. Bull. Jpn. 17* (1969) 2201.
7. Müller, H. *J. Chem. Soc.* (1915) 872; *Org. Synth. Coll. Vol. IV* (1963) 478.
8. Feuerstein, W. and von Kostanecki, St. *Chem. Ber. 31* (1898) 715.
9. Lövenbein, A. *Chem. Ber. 57* (1924) 1517.
10. Bedoukian, P. Z. *J. Am. Chem. Soc. 66* (1944) 1325.
11. Ziegenbein, W. and Franke, W. *Chem. Ber. 90* (1957) 2291.
12. Carlson, R. and Nilsson, Å. *Acta Chem. Scand., Ser. B 38* (1984) 49.
13. Schroll, R. and Bertsch, E. *Chem. Ber. 34* (1901) 1441.
14. Baker, W., Chadderton, J., Harborne, J. B. and Ollis, W. D. *J. Chem. Soc.* (1953) 1852.
15. Joshi, P. C. and Venkataraman, K. *J. Chem. Soc.* (1934) 513.

Received December 8, 1987.