Reaction of 2'-Hydroxychalcone with Hydrazoic Acid [1]

By **Sandro Cacchi** and **Gianni Palmieri**, Cattedra di Chimica Organica, V. Castro Laurenziano 9, Universita' di Roma, Italy
Domenico Misiti,* Istituto di Chimica Organica, Universita' di Camerino, Italy

Treatment of 2'-hydroxychalcone with hydrazoic acid in trifluoroacetic acid gave flavanone, 2,3-dihydro-2-phenyl-1,4-benzoxazepin-5(4*H*)-one, 2-styrylbenzoxazole, (±)-*trans*-3-aminoflavanone, and isoflavone. The mechanism of the reaction is discussed.

In connection with our studies on the synthesis of heterocyclic compounds by means of the Schmidt rearrangement,[2-5] we have investigated the reaction of 2'-hydroxychalcone (1) with hydrazoic acid. The reaction was carried out in trifluoroacetic acid (TFA) at room temperature and the following products were isolated and identified: flavanone (2) (5% yield), 2,3-dihydro-2-phenyl-1,4-benzoxazepin-5(4*H*)-one (3) (5%), 2-styrylbenzoxazole (4) (10%), (±)-*trans*-3-ammonioflavanone trifluoroacetate (6) (40%), and isoflavone (5) (30%) (see Scheme 1).

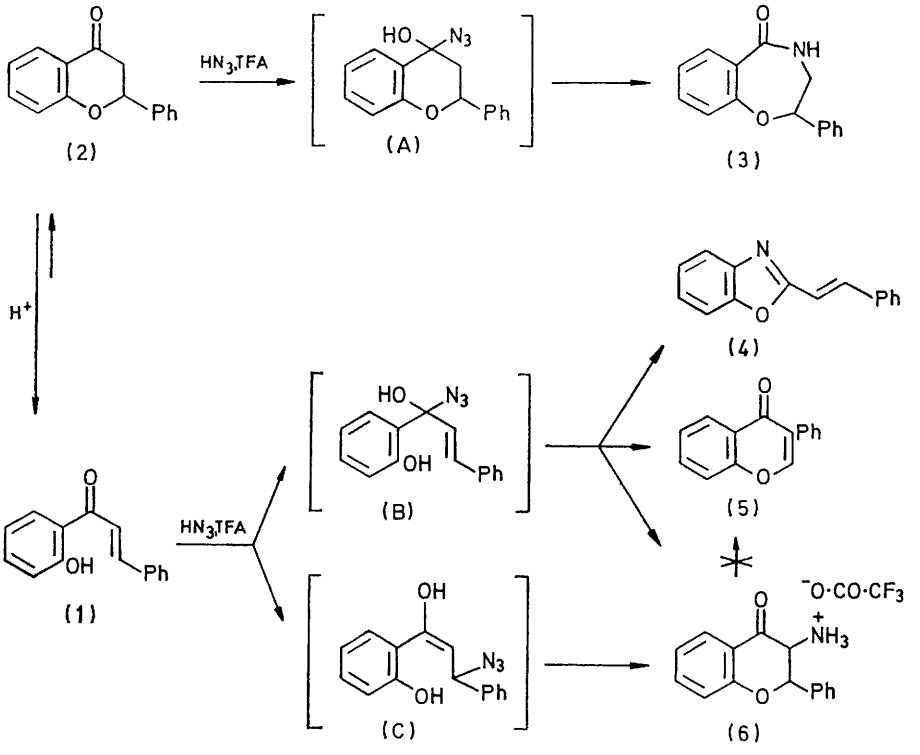
The reaction mechanism has not been studied in detail, but it appears likely that initial protonation of the carbonyl oxygen atom may be the driving force. Thus, the formation of the benzoxazepinone (3) is thought to proceed by way of the Schmidt rearrangement of flavanone (2),[2,5,6] derived from the acid-catalysed cyclization of 2'-hydroxychalcone.

On the other hand, initial protonation of the carbonyl oxygen atom may favour intermolecular 1,2- and/or 1,4-[7] addition of HN_3 to the αβ-unsaturated carbonyl

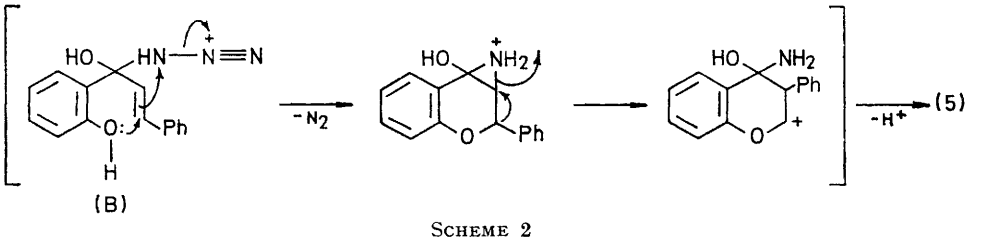
[1] Preliminary communication, D. Misiti, *Ann. Ist Sup. Sanita'*, 1973, **9**, 174.
[2] D. Misiti and V. Rimatori, *Tetrahedron Letters*, 1970, 947.
[3] D. Misiti and V. Rimatori, *Gazzetta*, 1971, **101**, 167
[4] D. Misiti, F. Gatta, and R. Landi-Vittory, *J. Heterocyclic Chem.*, 1971, **8**, 231.
[5] D. Misiti and V. Rimatori, *Ann. Ist Sup. Sanita'*, in the press.
[6] I. M. Lockhart, *Chem. and Ind.*, 1968, 1844.
[7] P. A. S. Smith, in 'Molecular Rearrangements,' ed. P. de Mayo, Interscience, New York, 1963, part I, p. 457; J. Mirek, *Bull. Acad. polon. Sci., Ser. Sci. chim.*, 1962, **10**, 421; *Zeszyty Nauk. Univ. Jagiellon, Pr. Chem.*, 1965, No. 10, 61 (*Chem. Abs.*, 1967, **66**, 37125[h]).

system in (1) to give the intermediates (B) and/or (C). The formation of the benzoxazole (4) can be ascribed to rearrangement of the intermediate (B) followed by elimination of water. In agreement with the general behaviour of aryl ketones [8] in the Schmidt reaction, particularly *o*-hydroxy-ketones,[9] this rearrangement proceeds with aryl migration.

The isoflavone skeleton is known to arise from oxidation of chalcone with thallium acetate [11] or lead tetra-acetate,[12] and from the reactions of flavanols with phosphorus trichloride [13] and of chalcone epoxides with boron trifluoride.[14] The mechanism of the reaction of chalcone epoxide with boron trifluoride–ether led us to the initial hypothesis that the isoflavone (5) obtained



SCHEME 1



SCHEME 2

The isoflavone (5) could also arise from the intermediate (B), by the pathway outlined in Scheme 2. This mechanism is a further example of flavanoid–isoflavanoid rearrangement through 1,2-phenyl migration, which is an essential step in the biosynthesis of isoflavones from chalcones.[10]

from the chalcone (1) with HN_3–TFA arose by the following pathway: 1,4-addition of HN_3 to the αβ-unsaturated carbonyl system to give the intermediate

[8] R. Fusco and S. Rossi, *Gazzetta*, 1951, **81**, 511.

[9] S. Palazzo and G. Mazzone, *Ann. Chim.* (*Italy*), 1958, **48**, 1329.

[10] E. Wong, *Chem. Comm.*, 1968, 365; *Phytochemistry*, 1968, **7**, 1751 and references therein; H. Grisebach, in ' Recent Advances in Phytochemistry,' ed. T. J. Mabry, R. E. Alston, and V. C. Runeckles, Appleton-Century-Crofts, New York, 1968, ch. 11; H. Grisebach, in ' Chemistry and Biochemistry of Plant Pigments,' ed. T. W. Goodwin, Academic Press, London, 1965, p. 279 and references therein; H. Grisebach and W. D. Ollis, *Experientia*, 1961, **17**, 4.

[11] W. D. Ollis, K. L. Ormand, and I. O. Sutherland, *Chem. Comm.*, 1968, 1237, *J. Chem. Soc.* (*C*), 1970, 119, 125.

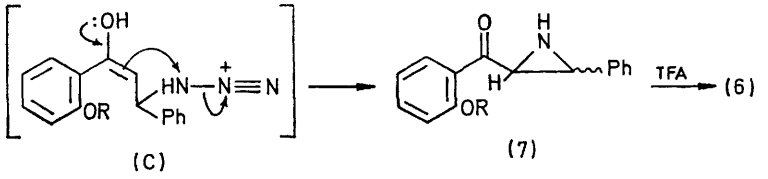
[12] G. W. K. Cavill, F. M. Dean, A. McGookin, B. M. Marshall, and A. Robertson, *J. Chem. Soc.*, 1954, 4573.

[13] J. W. Clark-Lewis and W. Korytnyk, *J. Chem. Soc.*, 1958, 2367; K. Freudenberg, G. Carrera, and E. Cohn, *Annalen*, 1926, **446**, 87.

[14] H. O. House, *J. Amer. Chem. Soc.*, 1956, **78**, 2298; H. O. House, D. J. Reif, and R. L. Wasson, *ibid.*, 1957, **79**, 2490; H. O. House and G. D. Ryerson, *ibid.*, 1961, **83**, 979; H. Grisebach and W. Barz, *Chem. Ber.*, 1964, **97**, 1688; H. Grisebach, in ' Recent Developments in the Chemistry of Natural Phenolic Compounds,' ed. W. Ollis, Pergamon, Oxford, p. 69; G. Litkey and R. Bognár, *Kemiai Kozlemenyek*, 1970, **34**, 249 and references therein.

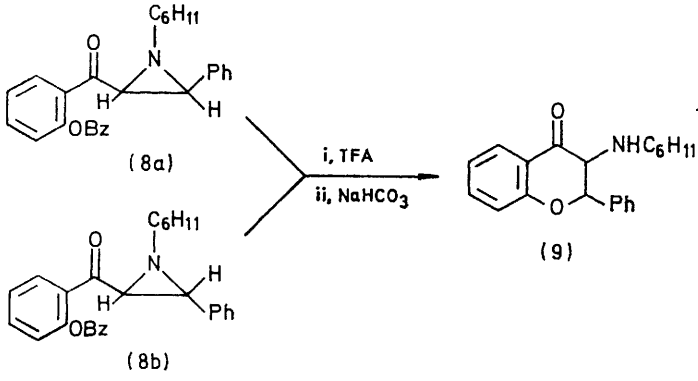
(C), elimination of nitrogen to give the aziridine (7), and acid-catalysed decomposition of (7) to (5). This route was supported by the known formation of *C*-acylaziridines by 1,4-addition of HN_3 to αβ-unsaturated ketones.[15]

In order to test this hypothesis we attempted the synthesis of the possible intermediate aziridine (7) by treating 2′-benzyloxychalcone * with ammonia and iodine, and also by treating 2′-benzyloxychalcone dibromide with ammonia.[17] Both these reactions gave the aziridine (7), isolated exclusively in the *trans*-form, and n.m.r. analysis of the reaction mixtures did not exhibit peaks attributable to the aziridine (7) in the *cis*-form. The *trans*-aziridine obtained, under reaction conditions which allow the conversion (1) ⟶ (5), does not give the isoflavone (5) but is quantitatively converted into (±)-*trans*-3-ammonioflavanone trifluoroacetate (6) (95% yield) (Scheme 3).



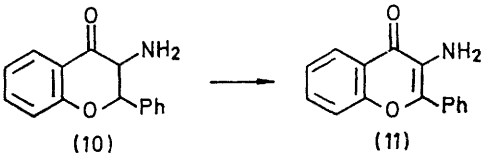
SCHEME 3

Since the corresponding *cis*-aziridine was not available, therefore we synthesized the *cis*-*N*-cyclohexylaziridine (8a)[16] as a model. This aziridine under the above conditions gives the *trans*-3-cyclohexylaminoflavanone (9) in an almost quantitative yield. The same result is achieved from the *trans*-aziridine (8b) (Scheme 4). We may therefore assume that the *cis*-isomer of (7) would behave in a similar manner, and these results thus enable us to exclude the aziridine (7) as an intermediate in the conversion (1) ⟶ (5).



SCHEME 4

The (±)-*trans*-3-aminoflavanone (10), obtained by mild treatment of the trifluoroacetate (6) with alkali, is stable to prolonged treatment with acids, but undergoes rapid and quantitative conversion into 3-aminoflavone (11) in methanolic sodium hydroxide (Scheme 5). This result is in agreement with the isolation of compound (11) from basic work-up [1] of the mixture obtained from the Schmidt reaction of 2′-hydroxychalcone. A similar aminoflavanone ⟶ aminoflavone conversion has been described previously.[17]



SCHEME 5

EXPERIMENTAL

M.p.s were determined with a Kofler apparatus. I.r. spectra were recorded with a Perkin-Elmer 21 and n.m.r. spectra with a Varian T-60 spectrometer (Me_4Si as internal standard).

Reaction of 2′-Hydroxychalcone with Hydrazoic Acid.—To a stirred solution of 2′-hydroxychalcone (2.00 g, 9 mmol) in trifluoroacetic acid (10 ml), sodium azide (0.850 g, 13.5 mmol) was added in small portions. The reaction, carried out at room temperature and under nitrogen, was complete after *ca.* 4 days.

Ether (150 ml) was added, and (±)-trans-3-*ammonioflavanone trifluoroacetate* (1.245 g, 40%) separated; m.p. 177—179 °C (Found: C, 57.95; H, 4.05; N, 4.0. $C_{17}H_{14}F_3NO_4$ requires C, 57.75; H, 4.0; N, 4.0%); $\nu_{max.}$ (Nujol) 1 695 cm^{-1} (C=O); δ ($CDCl_3$) 8.10—7.00 (9 H, m), 5.50 (1 H, d, *J* 12 Hz), 4.86 (1 H, d, *J* 12 Hz), and 4.85br (3 H, s). The ethereal layer was neutralized with carbonate solution, dried (Na_2SO_4), and evaporated. The oily residue (1.129 g) was separated by column chromatography (silica gel). Elution with ethyl acetate–n-hexane (2 : 8) gave the following products, identified by comparison with authentic specimens: flavanone (2) (0.097 g), 2,3-dihydro-2-phenyl-1,4-benzoxazepin-5(4*H*)-one (3) (0.190 g),[2] 2-styrylbenzoxazole [18] (4) (0.184 g), and isoflavone (5) (0.588 g).

Synthesis of trans-2-(2-*Benzyloxybenzoyl*)-3-*phenylaziridine* (7).—To a stirred solution of 2′-benzyloxychalcone (1.00 g, 3.18 mmol) in absolute methanol (20 ml) and saturated with dried (NaOH) ammonia, a solution of iodine in methanol (1.00 g in 14 ml) was added. The mixture was

* The need for the introduction of a protective group on O-2′ in the synthesis of aziridines from 2′-hydroxychalcones was reported recently.[16]

[15] A. J. Davies, A. S. R. Donald, and R. E. Marks, *J. Chem. Soc.* (*C*), 1967, 2109.

[16] G. Litkey, R. Bognár, P. Szigeti, and V. Trapp, *Acta Chim. Acad. Sci. Hung*, 1972, **73**, 95.

[17] G. Litkey, R. Bognár, and J. Andó, *Acta Chim. Acad. Sci. Hung*, 1973, **76**, 95.

[18] K. Nakagawa, H. Onoue, and J. Sugita, *Chem. and Pharm. Bull.* (*Japan*), 1964, **12**, 1135; W. G. Bywater, W. R. Coleman, O. Kamm, and H. Merritt, *J. Amer. Chem. Soc.*, 1945, **67**, 905; S. Skraup, *Annalen*, 1919, **419**, 1.

kept at room temperature under nitrogen until it turned colourless (*ca.* 6 h); it was then cooled to 5 °C and maintained at this temperature until the aziridine (0.700 g, 93%) crystallized [m.p. 105—107 °C (lit.,[17] 106—108 °C)]; it was identical (i.r. and n.m.r. spectra) with an authentic sample.

Decomposition of the trans-*Aziridine* (7).—A solution of the *trans*-aziridine (0.5 g, 2.14 mmol) in TFA (2 ml) was stirred at room temperature under nitrogen. After 1 h the starting material had disappeared, and only one new compound was formed. The latter was stable under the reaction conditions for several days. On addition of diethyl ether (100 ml) the ammonium salt (6) (m.p. 176—178 °C) crystallized (0.708 g, 95%) from the solution. A mixed m.p. determination did not show depression.

(±)-trans-3-*Cyclohexylaminoflavanone* (9).—A solution of *cis*-2-(2-benzyloxybenzoyl)-1-cyclohexyl-3-phenylaziridine [16] (8a) or of the *trans*-isomer (8b) (0.5 g, 1.22 mmol) in TFA (2 ml) was stirred at room temperature under nitrogen. After *ca.* 24 h the starting material had disappeared and diethyl ether was added. The ethereal layer was then washed with saturated aqueous sodium hydrogen carbonate and dried (Na_2SO_4) to give, after evaporation of the solvent, crude (±)-*trans*-3-cyclohexylaminoflavanone (9) (0.370 g, 95%) with spectral properties essentially identical with those of the pure material. Crystallization from aqueous ethanol gave the pure product (9) (0.335 g, 86%), m.p. 97—99 °C (lit.,[16] 98—100 °C).

(±)-trans-3-*Aminoflavanone* (10).—(±)-*trans*-3-Ammonioflavanone trifluoroacetate (6) (1.00 g, 2.87 mmol) was added to a mixture of diethyl ether (200 ml) and saturated aqueous sodium hydrogen carbonate (50 ml) with shaking. The separated organic layer was washed with water then dried (Na_2SO_4) and evaporated to give (±)-*trans*-3-aminoflavanone (10) (0.635 g, 97%) as an oil which slowly crystallized; m.p. 102—103 °C (lit.,[19] 106—108 °C); δ ($CDCl_3$) 8.00—6.80 (9 H, m), 5.03 (1 H, d, *J* 12 Hz), 4.00 (1 H, d, *J* 12 Hz), and 1.76 (2 H, s).

3-*Aminoflavone* (11).—To a solution of compound (6) (0.5 g, 1.44 mmol) in methanol (5 ml), methanolic 2% sodium hydroxide (5 ml) was added. After a few minutes the trifluoroacetate (6) had disappeared and the mixture was diluted with diethyl ether (100 ml). The ethereal layer was then washed with water, dried (Na_2SO_4), and evaporated to leave crude 3-aminoflavone (0.320 g, 93%) which was recrystallized from ethanol; m.p. 134—135 °C (lit.,[19] 138—139 °C), identical (i.r. and n.m.r. spectra) with an authentic sample.

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[19] M. Michalska, *Bull. Acad. polon. Sci. Sér. Sci. chim.*, 1968, **16**, 567 (*Chem. Abs.*, 1969, **70**, 87466[y]); R. Bognár and M. Rakosi, *Annalen*, 1966, **693**, 225 (*Chem. Abs.*, 1966, **65**, 8864[h]); A. Kasahara, *Nippon Kagaku Zasshi*, 1959, **80**, 416 (*Chem. Abs.*, 1961, **55**, 5481); R. Bognár, C. O'Brien, E. M. Philbin, U. Ushioda, and T. S. Wheeler, *Chem. and Ind.*, 1960, 1186.