BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 52 (2), 647—648 (1979)

Synthesis and Reduction of 3-Bromoflavanones

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(Received April 14, 1978)

Synopsis. Bromination of flavanone, 6-methylflavanone, 6-methyl-4′-methoxyflavanone, and 6-methyl-3′,4′-dimethoxyflavanone with pyridinium tribromide in glacial acetic acid gives the corresponding 3-bromoflavanones, which when refluxed with thiourea in ethanol undergo reduction to flavanones.

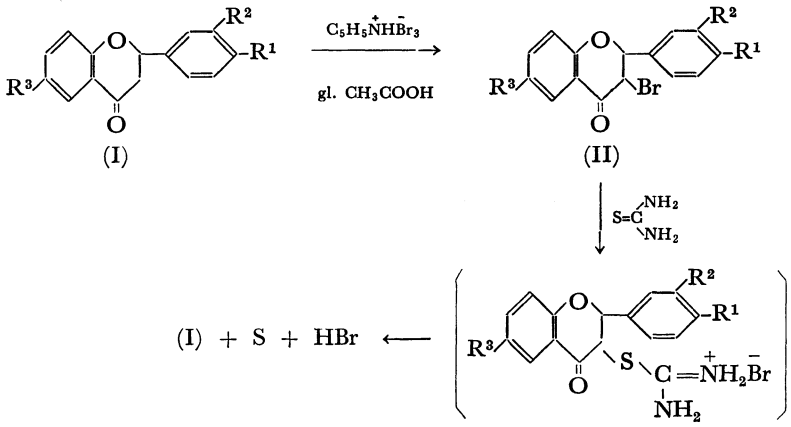
Several reagents such as pyridinium tribromide,[1] phenyltrimethylammonium tribromide,[2,3] 2-pyrrolidone hydrotribromide,[4] (2-carboxyethyl)triphenylphosphonium tribromide,[5] and 2-bromo-2-cyano-*N*,*N*-dimethylacetamide[6] have been employed for the selective bromination of C–H α to a carbonyl group. All these reagents, however, are not equally effective and their reactivity varies with the presence of other functional groups prone to bromine reactivity.

Because of the asymmetric centres, 3-bromoflavanones exist in two racemic forms having different configurations for C_3-bromine. These compounds have been synthesized by the bromination of flavanones with bromine dissolved in a suitable solvent[7–11] or with a brominating agent like dioxane dibromide,† [12] trimethylphenyl ammonium tribromide,[13] and *N*-bromosuccinimide.[10,14–16] 3-Bromoflavanones have also been obtained by the cyclization of 2′-acetoxychalcone dibromides[17–19,22] as well as of 2-bromo-3-ethoxy-1,3-diphenyl-1-propanone.[20] A 3-bromoflavanone was synthesized by the action of copper(II) bromide on 2′-hydroxychalcone.[21] All the methods gave a mixture of cis and trans isomers.

In the present work, we have brominated four variedly substituted flavanones (I) with pyridinium tribromide in acetic acid medium. Three cases gave only the trans isomer, whereas, in the case of 6-methyl-3′,4′-dimethoxyflavanone a mixture of *trans*- and *cis*-bromoflavanones has been obtained.

Keeping in view the biological importance of thio compounds, we examined the reaction of thiourea with 3-bromoflavanones (II). Thiourea reacts with α-halo ketones[24–27] and chalcone dibromides to afford the corresponding thiazoles and chalcones[28] respectively. However, under the reaction conditions employed, the 3-bromo-flavanones undergo conversion to the corresponding flavanones (I).

In addition to flavanone only sulfur could be isolated from the reaction mixture and a positive test was obtained for the presence of HBr. In the light of these facts, a likely reaction path can be as follows.



where
(a) $R^1=R^2=R^3=H$, (b) $R^1=H$; $R^2=H$, $R^3=CH_3$, (c) $R^1=OCH_3$; $R^2=H$; $R^3=CH_3$,
(d) $R^1=R^2=OCH_3$; $R^3=CH_3$

It may be mentioned that all the attempts to detect the presence of urea in the reaction mixture met with failure.

Experimental

All melting points are uncorrected. Pyridinium tribromide was prepared by following the reported procedure.[1]

trans-3-Bromoflavanone (IIa). Flavanone (Ia; 1.1 g) was dissolved in glacial acetic acid (5 ml) by warming on water-bath. To the hot solution was added pyridinium tribromide (1.6 g) in equimolar ratio in small amounts shaking the contents to expel the HBr formed. After the complete addition of the reagent, the reaction mixture was kept at room temperature for 30 min with occasional shaking. It was then diluted with cold water and 3-bromoflavanone thus obtained was crystallized from ethanol to give white crystals (0.9 g) mp 111—112 °C (lit,[12] mp 111 °C).

trans-3-Bromo-6-methylflavaone (IIb). Flavanone (Ib; 1 g) was dissolved in glacial acetic acid (5 ml) by warming on water-bath. To the hot solution was added pyridinium tribromide (1.5 g) under the conditions described above.

† *p*-Dioxane and bromine in equimolar ratio.

After 1/2 h crystals of 3-bromoflavanone separated, which were filtered, washed with water and recrystallized from ethanol to give white glistering leaflets (0.85 g) mp 127—128 °C (lit,[23] mp 127—128 °C). The dilution of the mother liquor gave (0.1 g) more of the product (IIb).
Found: C, 60.4; H, 4.3; Br, 25.1%. Calcd for $C_{16}H_{13}O_2Br$: C, 60.5; H, 4.1; Br, 25.23%.

trans-3-Bromo-4'-methoxy-6-methylflavanone (IIc). Flavanone (Ic; 1.3 g) was dissolved in glacial acetic acid (5 ml) by warming on water-bath. To the hot solution was added pyridinium tribromide (1.3 g) in small amounts. The reaction mixture was worked up as described for IIb. The solid thus obtained was crystallized from ethanol to afford white hexagonal plates (0.8 g) mp 141—142 °C (lit,[22] mp 138 °C).
Found: C, 58.6; H, 4.2; Br, 22.8%. Calcd for $C_{17}H_{15}O_3Br$: C, 58.7; H, 4.3; Br, 23.05%.

3-Bromo-3',4'-dimethoxy-6-methylflavanone (IId). Flavanone (Id, 1 g) was dissolved in glacial acetic acid (5 ml) by warming on water-bath. To the hot solution was added pyridinium tribromide (1 g) in small amounts. The reaction mixture was worked up as described for IIb. The solid thus obtained gave *cis*-3-bromo-3',4'-dimethoxy-6-methylflavanone as colourless plates (0.97 g), mp 158—159 °C (lit,[22] mp 155—156 °C) and *trans*-3-bromo-3',4'-dimethoxy-6-methylflavanone (0.21 g), mp 144—145 °C (lit,[22] mp 142—143 °C) from ethanol.
Found: C, 56.8; H, 4.4; Br, 21.6%. Calcd for $C_{18}H_{17}BrO_4$: C, 57.3; H, 4.5; Br, 21.2%.

Action of Thiourea on 3-Bromo-4'-methoxy-6-methylflavanone. A mixture of the bromoflavanone (1.7 g), thiourea (0.4 g) and ethanol (20 ml) was refluxed on water-bath for three hours. The reaction mixture was then allowed to cool to room temperature and poured into cold water. The solid thus separated was filtered and washed with water. Crystallization from ethanol afforded two products. The sparingly soluble compound on recrystallization from benzene gave yellow needles of free sulfur (0.1 g, mp 120 °C). The soluble product was found to be 4'-methoxy-6-methylflavanone (1.12 g), mp 109 °C (lit,[11] mp 108—109 °C). A mixed melting point determination with an authentic sample of flavanone showed no depression.

Action of Thiourea on 3-Bromoflavanone. A mixture of 3-bromoflavanone (1 g), thiourea (0.3 g), and ethanol (20 ml) was refluxed on water-bath for three hours. The reaction mixture was allowed to cool to room temperature and poured into cold water. The usual work up of the reaction mixture gave sulfur (0.04 g, mp 119—120 °C) and flavanone (0.62 g, mp 76 °C) (lit,[29] mp 76 °C). A mixture melting point determination with an authentic sample of flavanone showed no depression.

Action of Thiourea on 3-Bromo-6-methylflavanone. A mixture of the bromoflavanone (1.6 g), thiourea (0.5 g), and ethanol (20 ml) was refluxed on water-bath for three hours. The reaction products were worked up as usual to afford yellow needles of sulfur (0.12 g, mp 120 °C) and 6-methylflavanone (0.95 g), mp 104—105 °C (lit,[30] mp 105 °C). No depression was observed when a mixture melting point determination with an authentic sample was carried out.

Action of thiourea on 3-Bromo-3',4'-dimethoxy-6-methylflavanone. A mixture of the bromoflavanone (0.6 g), thiourea (0.3 g) and ethanol (20 ml) was refluxed on water-bath for three hours. The reaction product when worked up as described above gave sulfur (0.05 g, mp 120 °C) and 3',4'-dimethoxy-6-methylflavanone (0.34 g), mp 108 °C (lit,[11] mp 108—109 °C). The identity of flavanone was further confirmed by mixture melting point determination with an authentic sample.

Authors are thankful to Prof. M. M. Bokadia for providing laboratory facilities and to U. G. C. (New Delhi) for the award of Junior Research Fellowship to (N. J. Reddy).

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