197. New Indigo Syntheses

Preliminary Communication

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Dedicated to Professor *R. B. Woodward*
on the occasion of his sixtieth birthday anniversary

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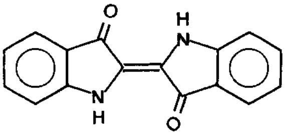
Summary

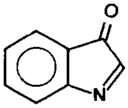
Three novel routes for the preparation of the dyestuff indigo are described. Two of the methods use isatoic anhydride, the third one styrene as starting materials. Key reactions are acylation of both dimsyl and nitromethane anions, *Pummerer* rearrangement and *Nef* reaction. A novel nitration of styrene is the basis of the third method.

The popularity of certain fashion wear has led to a vigorous comeback of the vat dye indigo **1** in recent years. This coloring matter, known for some fourty centuries, was originally obtained from plants of *Indigofera* species. *Baeyer*'s determination of the constitution and first synthesis [1a, b] gave rise to a period of frantic search for practical syntheses in the chemical industry of the time [2]. The end was most successfully achieved by *Heumann*'s indoxyl melt process of 1890 [2] [3], nowadays in much improved version, still the method practised on large scale.

3*H*-Indol-3-one (**2**), recognized as most likely though elusive intermediate in syntheses of indigo [1c] suggested novel approaches to the dye to be described herein.

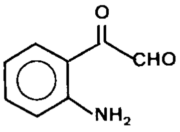


1



2

An equally fugitive compound and hence undescribed in the literature is the hypothetical hydrolysis product of **2**, *o*-aminophenylglyoxal (**3**). The corresponding dimethyl acetal, however, can be prepared and it rapidly and quantitatively converts to indigo on acidic hydrolysis [4]. The approaches to **3** to be outlined first feature as common idea the combination of the two synthons anthranoyl cation **4** (bearing a protecting group on nitrogen to prevent self-condensation) and formyl anion **5**.



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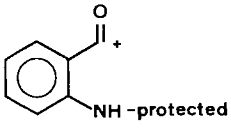


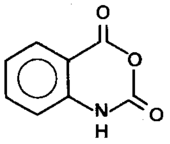
4

$\overset{-}{\mathrm{C}}\mathrm{HO}$

5

Isatoic anhydride **6** seemed an attractive precursor of **4**, comprising both activation of the desired carbonyl function and protection at the NH-group. Moreover, deprotection could be expected to involve no extra step other than acidic work-up. The anion of dimethylsulfoxide (dimsylanion) was chosen as the masked form of **5**; it had previously been used in acylation reactions with esters of aromatic carboxylic acids [5].

Thus, when a dimethylsulfoxide solution (*ca.* 7%) of **6** was added in a nitrogen atmosphere to a solution of dimsyl sodium (3 equivalents) in the same solvent at room temperature *o*-amino-ω-methylsulfinylacetophenone (**7**)[1][2], m.p. 102–103°, was formed in 82% yield.



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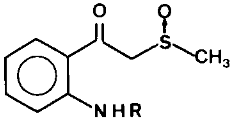

7 R = H
8 R = $COCH_3$

Pummerer rearrangement of **7**, effected by warming its aqueous hydrochloric acid solution, was followed by loss of methyl mercaptan and gradual formation of precipitating indigo. The ethanol-washed and dried dye resulted in 39% yield. A more satisfactory yield was obtained when **7** was acetylated in benzene solution with acetic anhydride at 80° to give **8**, m.p. 140–141°, in 86% yield[1][3]. Acid treatment of **8** (1% solution in 1 N HCl, 90°, 15 min) afforded **1** in 77% yield. The dye-forming reaction can also be carried out on the garment or fiber. Moreover, formation of the dye on the fabric by acidic development opens the way to a novel printing technique.

Although not hitherto used as formyl anion (**5**) synthon, the readily available nitromethane was found to serve as a good source for this functionality. Reports in the literature on C-acylation of nitroalkanes are scarce [6] and the only procedure in which the use of an anhydride is described [6a] proved unacceptable due to low yield.

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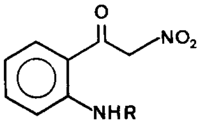
[1] Correct microanalytical values and spectroscopic data in accordance with the proposed structure were obtained of all new compounds.

[2] Upon completion of this work (Swiss patent application filed December 24, 1975) the author became aware of the description of **7** in U.S. pat. 3937704 (*M. von Strandtmann, J. Shavel, Jr., S. Klutchko & M. Cohen,* issued February 10, 1976).

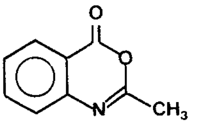
[3] In the mother-liquors of **8** its rearrangement product *o*-acetamino-ω-methylmercapto-ω-acetoxyacetophenone can be recognized spectroscopically (estimated yield: 7%). This compound was the major product under more drastic acetylation conditions. It, too, was transformed into **1** in 55% yield when its aqueous-methanolic hydrochloric acid solution was warmed.

However, when **6** was reacted with two equivalents of nitromethane in dimethylsulfoxide solution at 50° for 12 h in the presence of 0.6 equiv. of anhydrous potassium carbonate *o*-amino-ω-nitroacetophenone[1] (**9**), m.p. 110–111°, was obtained in 57% yield[4]. On warming **9** in 4 N aqueous HCl initial darkening followed by precipitation of **1** was observed. Doubtless, the key step of this transformation is a *Nef* reaction in the course of which the nitromethyl group of **9** is converted to a carboxaldehyde function or an equivalent thereof. Both in terms of yield and purity of **1**, the conversion **9** to **1** is again advantageously carried out with intercalary acetylation of the amino group. **10**[1], m.p. 180–182°, was prepared by heating a benzene solution of **9** containing acetic anhydride. When crude **10** obtained by evaporation of solvent and excess reagent was warmed in 2 N HCl to 75–80° for 3 h **1** was isolated in 88% yield from **9**.



9 R = H
10 R = $COCH_3$

Alternatively, **10** could be prepared from 2-methyl-1,3-benzoxazin-4-one, **11** [7], albeit in low yield, by treating **11** in hexamethylphosphoric amide solution at 80° with two equivalents of nitromethane in the presence of anhydrous sodium carbonate. The main product of the reaction was found to be the anthranilic acid derivative **12**[1], m.p. 168–170°. It appears that **11** reacts only partially in the sense predicted for expression **4**.



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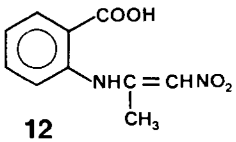

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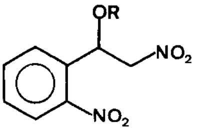
Still another route to **1** was hinted by the finding of *Harley-Mason* [8] that the dinitro-hydroxy derivative **13** yields indigo in high yield when reduced with aqueous sodium dithionite. **13** had been obtained previously by *Thiele* [9] from *o*-nitrobenzaldehyde. This author also had noted the formation of a blue color on treatment of **13** with ferrous ions.



13 R = H
14 R = $COCH_3$

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[4] **9** proved somewhat unstable under the conditions of the experiment and, in particular, in strongly basic media. When **9** was warmed in aqueous 1 N sodium hydroxide anthranilic acid was formed rapidly in a manner reminiscent of the haloform cleavage.

It seemed an intriguing task to introduce all the functionalities of **13** in one reaction starting from styrene. There exist reports on nitrations of this hydrocarbon [10], but the products isolated are not suitable for conversion into **1**. The dinitroacetate **14**, m.p. 109–111°, however, could be obtained directly in 42% yield (determined by NMR.-spectroscopy) when styrene was nitrated with a mixture of acetic anhydride and nitric acid (d = 1.4) [10b] in the presence of a catalytic amount of conc. sulfuric acid at 5–14° for 4 h using a molar ratio nitric acid/styrene of 4.3. The desired product, identical with an authentic sample prepared according to *Thiele* [9], crystallized partially from an ether solution of the crude reaction product. Transesterification in boiling methanol in the presence of *p*-toluenesulfonic acid converted **14** into **13**, which, when treated without purification in dilute aqueous sodium hydroxide at 15° with sodium dithionite [8] yielded **1** in 59% yield from **14**.

The diligent, patient and highly skilled technical assistance of Mr. *Eugen R. Boss* of *Ciba-Geigy* Limited is gratefully acknowledged.

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