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New method for the preparation of 3-diazo-1,3-dihydroindol-2-ones*

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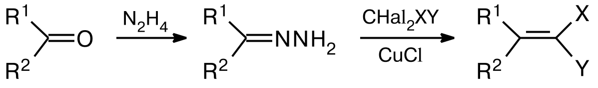
A new method for the preparation of diazo compounds of 2-indolinone series by oxidation of isatin hydrazones with polyhaloalkanes in the presence of copper salts in catalytic amounts was developed.

Key words: catalytic olefination reaction, polyhaloalkanes, copper salts, isatin, oxidation, catalysis, diazo compounds.

Earlier,[1] we have found and extensively studied a new reaction allowing us to form a C=C double bond, *viz.*, the catalytic olefination reaction. This reaction of polyhaloalkanes with *N*-unsubstituted hydrazones catalyzed with copper salts allows one to efficiently obtain a wide range of different alkenes (Scheme 1).

Scheme 1



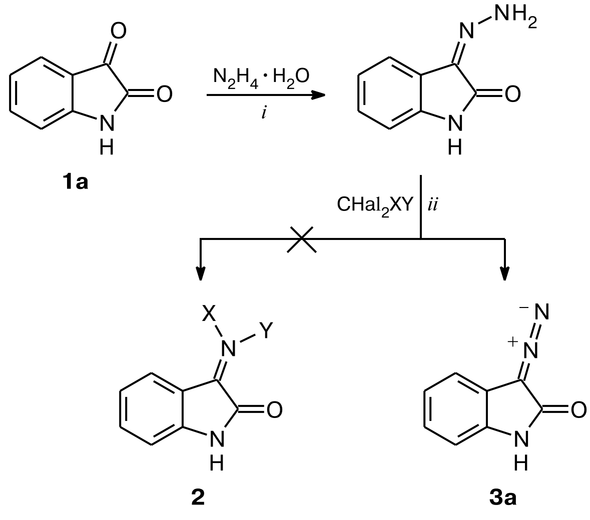
R^1 = Ar, Alk; Hal = Cl, Br; X = F, Cl, Br, H
R^2 = Alk, H; Y = F, Cl, Br, CN, CO_2Et, CF_3, CF_2Cl, CF_2Br

The reaction has a general character, hydrazones of aliphatic, aromatic, and heteroaromatic aldehydes and ketones and a wide range of polyhaloalkanes can be used.[1] In some cases, the reaction followed an abnormal route leading to the formation of saturated compounds (without a formation of olefination products[2]).[3]

In the present work, we studied another unusual transformation occurring under conditions of the catalytic olefination reaction, *viz.*, the formation of the corresponding diazo alkanes from hydrazones of isatin and its derivatives.

Introducing the isatin hydrazone obtained from isatin **1a** into the catalytic olefination reaction, we expected to develop an approach to the synthesis of the corresponding dihaloalkenes **2**, which have several reaction centers and are of high interest in the synthesis of isatin derivatives.[4] However, when carbon tetrachloride was used in the olefination of isatin hydrazone under standard conditions (DMSO, aqueous ammonia, 2% CuCl), diazo amide **3a** was obtained in 85% yield instead of the expected dichloroalkene **2** (Scheme 2). Similar result was also obtained in

Scheme 2



i. EtOH, reflux; *ii.* NH_3, DMSO, 2% CuCl.

PHA	Yield of **3a** (%)	PHA	Yield of **3a** (%)
CCl_4	85	CBr_4	72
$CHBr_3$	83	CF_3CBr_3	69

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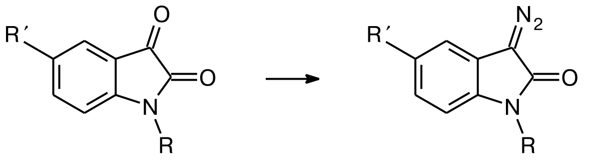
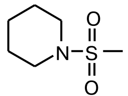
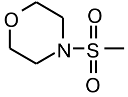
the case of other polyhaloalkanes (PHA), however, the use of CCl_4 has proved to be the most effective for isolation and purification of the desired reaction products.

In order to study the scope and limitations of this method, we have used other substrates of the isatin series **1** containing substituents at the nitrogen atom or functional groups of different nature at position 5. It turned out that this method has a general character, and the corresponding diazo compounds **3** can be obtained under mild conditions and in high yields (Scheme 3). To sum up, the polyhaloalkane—copper chloride—ammonia system serves as an efficient oxidant of hydrazones into diazo compounds.

Scheme 3

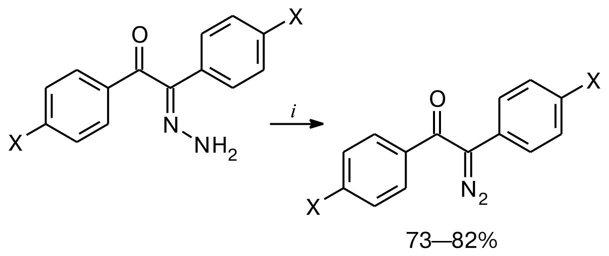


1a—i **3a—i**

Compound	R	R′	Yield **3** (%)
a	H	H	85
b	Me	H	86
c	Bn	H	71
d	H	F	52
e	H	Cl	53
f	H	NO_2	73
g	H	MeO	46
h	H		69
i	H		47

Earlier,[5] unsubstituted hydrazones of carbonyl compounds were oxidized into diazo alkanes with mercury oxide, lead tetraacetate, iodonium salts, and iodoso compounds, as well as with other inorganic and organic oxidants. Copper salts (like many transition metal salts) effectively catalyze decomposition of diazo alkanes with liberation of the nitrogen molecule.[6] There was only one work[7], where copper(II) acetylacetonate was used as a catalyst in oxidation of a number of keto hydrazones to the corresponding diazo ketones with air oxygen at 0—5 °C (Scheme 4).

Scheme 4

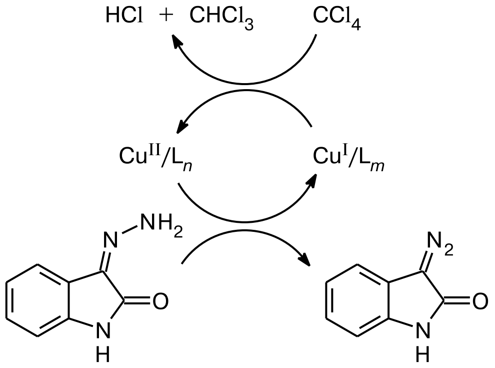


i. $Cu(acac)_2$, 10%, Et_2O, 0—5 °C, 20—45 min, O_2.

X = H, Me, Cl, MeO

Mechanism of the reaction was not discussed in this work, however, it can be suggested that a divalent copper is the true oxidant, air oxygen is the cooxidant. Apparently, in our case a divalent copper is also the true oxidant of hydrazone to diazoamide (Scheme 5). The role of polyhaloalkane consists in the regular regeneration of Cu^{2+}, *i.e.*, it plays the role of cooxidant in this reaction. Ammonia, as in the catalytic olefination reaction, plays the role of a ligand and acceptor of the liberated hydrogen halide. It should be noted that the mild oxidation conditions contribute to high yields of the corresponding diazo compounds even in the presence of copper salts.

Scheme 5



L = NH_3

Earlier, diazo compounds of the 2-indolinone series **3** have been obtained by oxidation of unsubstituted hydrazones with mercury oxide[8] or lead tetraacetate,[9] by the reaction of 2-indolone (oxyindole) with sulfonylazides,[10] however, the most widely used method is decomposition of isatin tosylhydrazones upon the action of aqueous alkali.[11]

The results obtained are the second example of the copper salt catalyzed oxidation of unsubstituted hydrazone to diazo compound, providing preparative yields. This method of the synthesis of diazo compounds is likely to have a great potential and opens wide synthetic possibilities, and we are planning further, more detailed studies of this interesting oxidation system.

Experimental

^1H and ^{13}C NMR spectra were recorded on a Bruker AMX 400 spectrometer (400.1 MHz and 100.6 MHz, respectively) in $CDCl_3$ and DMSO-d_6 using $SiMe_4$ as an internal standard.

IR spectra were recorded on an UR-20 spectrophotometer for neat samples. TLC analysis was performed on Silufol UV-254 plates, visualizing in acidified aqueous $KMnO_4$, in iodine vapor, or under the UV light. Column chromatography was performed on Merck silica gel (63—200 mesh). The starting compounds **1b**,**c** (see Ref. 12) and **1d**—**i** (see Ref. 13) were obtained according to the procedures described earlier. The ^1H and ^{13}C NMR spectra of compounds **3a** (see Ref. 14) and **3b**,**c** (see Ref. 15) agree with those given in the literature.

Synthesis of 3-diazo-1,3-dihydro-2*H*-indol-2-ones 3 (general procedure). A hot solution of the corresponding isatin **1** (5 mmol) in ethanol (50 mL) was poured to hydrazine hydrate (0.275 mg, 5.5 mmol) in ethanol (10 mL). The reaction mixture was refluxed for 1—3 h (TLC monitoring), followed by evaporation of ethanol *in vacuo*. Then, dimethyl sulfoxide (20 mL), 25% aq. ammonia (2 mL, ~25 mmol), and CuCl (10 mg, 2 mol.%) were added, and after stirring the mixture for 5 min, CCl_4 (2.5 mL, 25 mmol) was poured at room temperature. This reaction mixture was stirred for 1 day, poured into water (300 mL), extracted with dichloromethane (3×50 mL), and dried with magnesium sulfate. Dichloromethane was evaporated *in vacuo* on rotary evaporator, the residue was purified by passing through a filter with silica gel, using dichloromethane or the dichloromethane—methanol (50 : 1) mixture as an eluent.

3-Diazo-1,3-dihydro-2*H*-indol-2-one (3a). The yield was 0.676 g (85%), a red powder, m.p. 166—168 °C (Ref. 16: 168 °C). IR, ν/cm^{-1}: 1680 (NHC=O), 2089 (C=N_2).

3-Diazo-1-methyl-1,3-dihydro-2*H*-indol-2-one (3b). The yield was 0.749 g (86%), a reddish orange powder, m.p. 88—89 °C (Ref. 15: 88—90 °C).

3-Diazo-1-benzyl-1,3-dihydro-2*H*-indol-2-one (3c). The yield was 0.878 g (71%), an orange powder, m.p. 85—87 °C (Ref. 15: 84—86 °C). IR, ν/cm^{-1}: 1672 (NHC=O), 2120 (C=N_2).

3-Diazo-5-fluoro-1,3-dihydro-2*H*-indol-2-one (3d). The yield was 0.464 g (52 %), a brownish yellow powder, m.p. 206—207 °C (Ref. 17: 209—210 °C). IR, ν/cm^{-1}: 1687 (NHC=O), 2096 (C=N_2). ^1H NMR (DMSO-d_6), δ: 6.81—6.92 (m, 2 H); 7.34—7.38 (m, 1 H); 10.66 (s, 1 H, NH). ^{13}C NMR (DMSO-d_6) δ: 61.6 (C=N_2); 107.1 (d, *J* = 27.8 Hz); 110.9 (d, *J* = 8.8 Hz); 112.0 (d, *J* = 24.2 Hz); 119.0 (d, *J* = 11.3 Hz); 129.4, 158.1 (d, *J* = 234.9 Hz); 168.1 (NHC=O).

5-Chloro-3-diazo-1,3-dihydro-2*H*-indol-2-one (3e). The yield was 0.507 g (53%), a brownish yellow powder, m.p. 189—191 °C. IR, ν/cm^{-1}: 1710 (NHC=O); 2120 (C=N_2). ^1H NMR (DMSO-d_6), δ: 6.87 (d, 1 H, *J* = 8.4 Hz); 7.08 (dd, 1 H, *J* = 8.4 Hz, *J* = 2.1 Hz); 7.53 (d, 1 H, *J* = 2.1 Hz); 10.75 (s, 1 H, NH). ^{13}C NMR (DMSO-d_6), δ: 60.7 (C=N_2); 111.0, 119.0, 119.1, 124.7, 125.2, 131.4, 167.4 (NHC=O). Found (%): C, 49.54; H, 2.04; N, 21.78. $C_8H_4ClN_3O$. Calculated (%): C, 49.63; H, 2.08; N, 21.71.

3-Diazo-5-nitro-1,3-dihydro-2*H*-indol-2-one (3f). The yield was 0.749 g (73%), a yellow powder, m.p. 237—239 °C (Ref. 18: 238—240 °C). IR, ν/cm^{-1}: 1355, 1520 (NO_2); 1710 (NHC=O); 2155 (C=N_2). ^1H NMR (DMSO-d_6), δ: 7.08 (d, 1 H, *J* = 8.7 Hz); 8.04 (dd, 1 H, *J* = 8.7 Hz, *J* = 2.3 Hz); 8.50 (d, 1 H, *J* = 2.3 Hz); 11.38 (s, 1 H, NH).

3-Diazo-5-methoxy-1,3-dihydro-2*H*-indol-2-one (3g). The yield was 0.250 g (46%), a red powder, m.p. 137—138 °C. IR, ν/cm^{-1}: 1700 (NHC=O); 2110 (C=N_2). ^1H NMR (DMSO-d_6), δ: 3.72 (s, 3 H, MeO); 6.66 (dd, 1 H, *J* = 8.4 Hz, *J* = 2.4 Hz); 6.80 (d, 1 H, *J* = 8.4 Hz); 7.10 (d, 1 H, *J* = 2.4 Hz); 10.46 (s, 1 H, NH). ^{13}C NMR (DMSO-d_6), δ: 55.9 (MeO); 61.1 (C=N_2); 105.7, 110.9, 111.8, 118.5, 126.8, 155.1, 168.3 (NHC=O). Found (%): C, 57.14; H, 3.73; N, 22.21. $C_9H_7N_3O_2$. Calculated (%): C, 56.87; H, 3.91; N, 21.98.

3-Diazo-5-piperidinosulfonyl-1,3-dihydro-2*H*-indol-2-one (3h). The yield was 1.063 g (69%), a brownish yellow powder, m.p. 190—191 °C. IR, ν/cm^{-1}: 1680 (NHC=O); 2120 (C=N_2). ^1H NMR (DMSO-d_6), δ: 1.29—1.38 (m, 2 H, CH_2); 1.48—1.58 (m, 4 H, 2 $NCH_2\underline{CH_2}$); 2.81—2.90 (m, 4 H, 2 $N\underline{CH_2}CH_2$); 7.09 (d, 1 H, *J* = 8.3 Hz); 7.43 (dd, 1 H, *J* = 8.3 Hz, *J* = 1.6 Hz); 7.88 (d, 1 H, *J* = 1.6 Hz); 11.14 (s, 1 H, NH). ^{13}C NMR (DMSO-d_6), δ: 23.4 (CH_2); 25.2 ($NCH_2\underline{CH_2}$); 47.1 ($N\underline{CH_2}CH_2$); 61.7 (C=N_2); 110.1, 118.6, 119.1, 125.3, 128.3, 136.5, 168.0 (NHC=O). Found (%): C, 50.81; H, 4.68; N, 17.99. $C_{13}H_{14}N_4O_3S$. Calculated (%): C, 50.97; H, 4.61; N, 18.29.

3-Diazo-5-morpholinosulfonyl-1,3-dihydro-2*H*-indol-2-one (3i). The yield was 0.717 g (47%), a brownish yellow powder, m.p. 245—247 °C. IR, ν/cm^{-1}: 1680 (NHC=O); 2120 (C=N_2). ^1H NMR (DMSO-d_6), δ: 2.81—2.90 (m, 4 H, 2 NCH_2); 3.60—3.67 (m, 4 H, 2 OCH_2); 7.11 (d, 1 H, *J* = 8.2 Hz); 7.45 (dd, 1 H, *J* = 8.2 Hz, *J* = 1.7 Hz); 7.89 (d, 1 H, *J* = 1.7 Hz); 11.17 (s, 1 H, NH). ^{13}C NMR (DMSO-d_6), δ: 46.4 (NCH_2); 61.8 (C=N_2); 65.8 (OCH_2); 110.2, 118.8, 119.3, 125.6, 127.1, 136.8, 168.0 (NHC=O). Found (%): C, 46.79; H, 3.89; N, 18.07. $C_{12}H_{12}N_4O_4S$. Calculated (%): C, 46.75; H, 3.92; N, 18.17.

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