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Facile Synthesis of Hydrazonyl Halides by Reaction of Hydrazones with *N*-Halosuccinimide–Dimethyl Sulfide Complex

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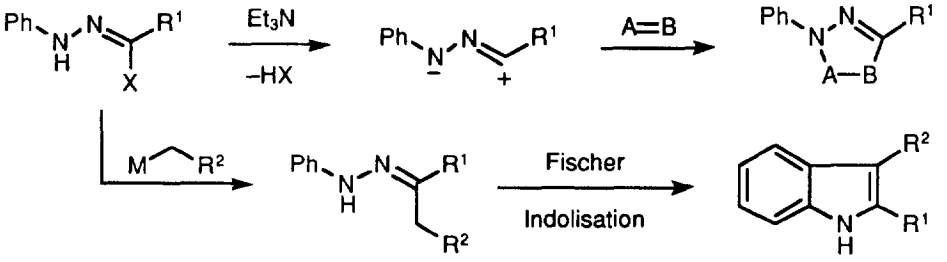
Abstract: A new and convenient method is described for the synthesis of hydrazonyl halides. Hydrazones on treatment with *N*-chlorosuccinimide–dimethyl sulfide complex result in the formation of the corresponding hydrazonyl chlorides in good yields. Similarly, treatment of hydrazones with *N*-bromosuccinimide–dimethyl sulfide complex gives the corresponding hydrazonyl bromide under extremely mild conditions.

Hydrazonyl halides have been the subject of considerable attention during the last few decades. They are considered to be important precursors of nitrile imines, which are used extensively in 1,3-dipolar cycloaddition reactions[1]—one of the most versatile methods for the construction of manifold 5-membered heterocycles[2] (Scheme 1). They can also be used to synthesise hydrazones of complex aliphatic ketones directly, by reaction with alkylmetal reagents (R^2CH_2M = Li, Zn, Mg, etc, Scheme 1). These hydrazones are important precursors of indoles in the Fisher Indolisation.[3]



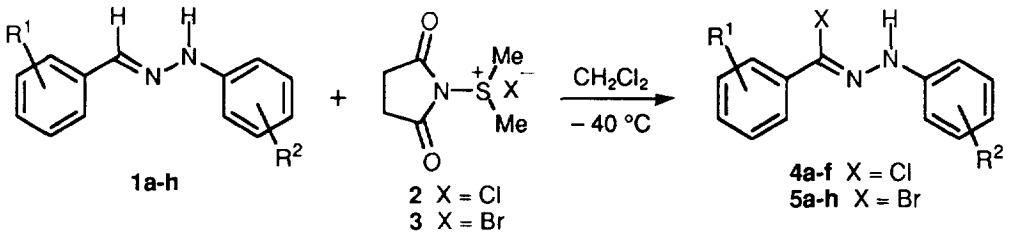
Scheme 1

In the course of our investigation on synthesis of functionalised indoles, a simple and convenient method for the synthesis of hydrazones of complex ketones was required. We felt that *N*-arylhydrazonyl halides would be ideal precursors. Literature search revealed that there

is no satisfactory method for their synthesis. The conventional methods for the synthesis of hydrazonyl halides include the action of phosphorous pentachloride on *N'*-benzoyl-*N*-arylhydrazines,[4] and halogenation of benzaldehyde hydrazones.[4,5,6] The applicability of these methods is limited. The first method can only be applied for the synthesis hydrazonyl chlorides, not bromides; the second is accompanied by halogenation in the *N*-aryl part of the hydrazone unless the aryl nucleus is deactivated.[4] Preparation of *N*-arylalkanehydrazonyl chlorides using the usual chlorinating agents, such as phosphoryl chloride,[7] phosphoryl chloride–pyridine,[8] phosphorous pentachloride,[9] or thionyl chloride[7] was unsuccessful. Wolkoff,[10] and more recently Kikugawa and Sakamoto,[11] has reported that action of the triphenylphosphine–carbon tetrachloride system on aryl hydrazides gives the corresponding hydrazonyl halides. This method, although more satisfactory than the others, is of limited value because it requires starting compounds that are difficult to obtain; acylation of hydrazines is not selective. We thus felt the need to develop an efficient method for the synthesis of hydrazonyl halides from easily available precursors. Herein we describe our finding in this direction.

Results

Our new method for the synthesis of hydrazonyl halides involves the action of halosulfonium salts on hydrazones. The *N*-chlorosuccinimide/*N*-bromosuccinimide–dimethyl sulfide complex, the Corey–Kim reagent,[12] a very reactive species, is stable at low temperatures. It can be conveniently prepared *in situ*, by addition of dimethyl sulfide to a solution of *N*-chlorosuccinimide (NCS) or *N*-bromosuccinimide (NBS) at 0 °C. Treatment of this complex **2** with benzaldehyde phenylhydrazone **1a** at –40 °C resulted in the formation of hydrazonyl chloride **4a**. Conversion was complete within 30 min. and compound **4a** was the only product formed (84%, Scheme 2).



Scheme 2

Aryl hydrazones **1b–f** possessing a variety of substituents in the aromatic nucleus were converted to the corresponding hydrazonyl chlorides **4b-f** in 61–81% yields (Table 1) under similar conditions. This shows that substitution in the phenyl ring of the starting hydrazones exerts no influence on the halogenation; this method can thus be considered to be fairly

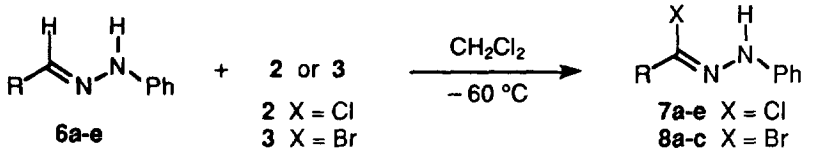
general. Similarly, treatment of hydrazones **1a–h** with complex **3**, generated by the action of Me_2S on NBS, afforded hydrazonyl bromides **5a–h** in 76–83% yields (Table 1).

Table 1 Yield and physical data of compounds **4** and **5**

Compd. No.	R^1	R^2	Yield (%)[a]	m.p. (Lit) (°C)[b]
4a	H	H	84	128–130 (129–131)[10]
4b	H	4-OMe	81	90–91 (91–92)[18]
4c	H	2-Me	79	65–66 (64.5–66)[19]
4d	H	4-NO_2	73	192–193 (189–192)[10]
4e	4-NO_2	H	71	156–157 (157–158.5)[19]
4f	4-OMe	H	61	133–134 (132–134)[20]
5a	H	H	83	109–111 (109–111)[10]
5f	3-NO_2	4-Br	80	145–146 (146.5)[5]
5g	3-NO_2	4-Cl	78	131–132 (133)[5]
5h	4-NO_2	4-Br	76	221–222 (224)[5]

[a] Yield of isolated product, [b] Uncorrected

Phenyl hydrazones of aliphatic aldehydes **6a–e** react similarly with halosulfonium salts **2** and **3** to give the corresponding *N*-phenylalkanehydrazonyl chlorides **7** a–e and bromides **8a–c**, respectively, in good yields (Scheme 3, Table 2).



Scheme 3

Table 2 Yield and physical data of compounds **7** and **8**

Compd. No.	R	X	Yield (%)[a]	m.p. (Lit) (°C)[b]
7a	$MeCH_2$	Cl	69	oil[11]
7b	$PhCH_2$	Cl	41	oil
7c	$PhCH_2CH_2$	Cl	71	oil[11]
7d	PhCH=CH	Cl	29	149–151(150–152)[11]
7e	$Me(CH_2)_6$	Cl	69	oil[11]
8a	$MeCH_2$	Br	62	oil
8b	$PhCH_2$	Br	38	oil
8c	$PhCH_2CH_2$	Br	67	oil

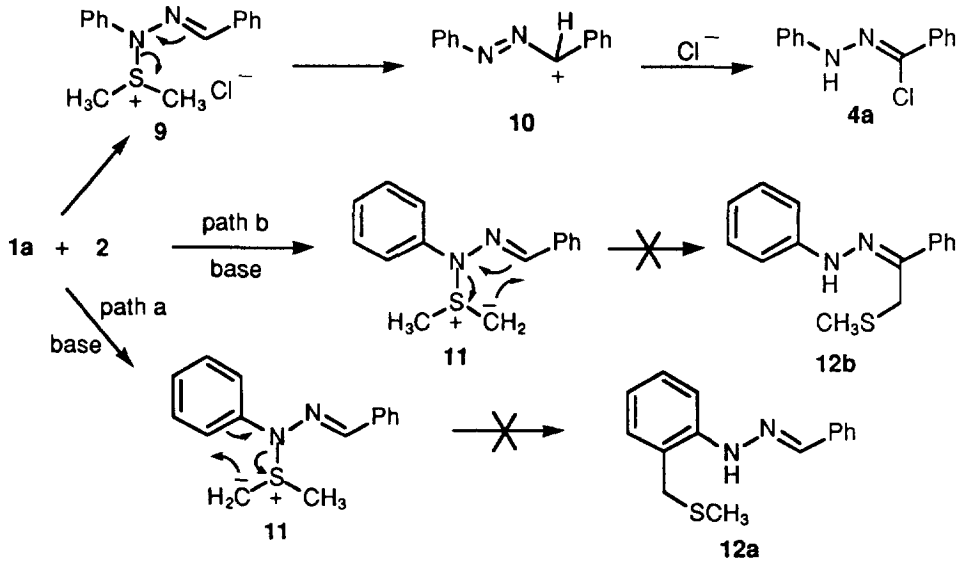
[a] Yield of isolated product, [b] Uncorrected

Discussion

The NCS/NBS–Me_2S complex (Corey–Kim reagent) has been used for the oxidation of alcohols to carbonyl compounds;[12] for the conversion of allylic and benzylic alcohols to the corresponding halides.[13] It has also been employed for the conversion of aldoximes to nitriles,[14] of acids to the corresponding methyl thiomethyl esters,[15] and in various transformations involving Sommlett–Hauser type rearrangements.[16] We demonstrate here its use in the halogenation of hydrazones.

Halogenation of hydrazones is an old and a commonly used method for obtaining hydrazonyl halides.[4,5,6] However, unless the nucleus is deactivated, halogenation of the aromatic ring invariably precedes that of the carbonyl carbon.[4] Our method results in clean and efficient conversion to hydrazonyl halides. The halogen does not enter the aromatic nucleus even in cases where the aromatic ring possesses electron-donating substituents such as *p*-OMe (**4f**). This is because halosulfonium salts **2** and **3**, unlike Cl_2 or Br_2, are *not* electrophilic halogenating agents. Another advantage associated with our method is the low reaction temperatures (–60 °C in contrast to other methods which necessitate reflux) at which side reactions, if any are suppressed. This method can be applied for the synthesis of a variety of hydrazonyl halides, including aliphatic, aromatic, substituted aromatic, and even "activated" aromatic.

A probable mechanism, exemplified for the formation of **4a** from **1a**, is depicted in Scheme 4. The first step can be assumed to be nucleophilic attack of the acidic N–H of hydrazone **4a** on halosulfonium ion **2** to give intermediate **9**. The mechanism originally proposed by Corey and coworkers[13] for the conversion of allyl, benzyl and trityl alcohols to the corresponding halides inv 'ved first, the formation of the oxysulfonium ion, which undergoes



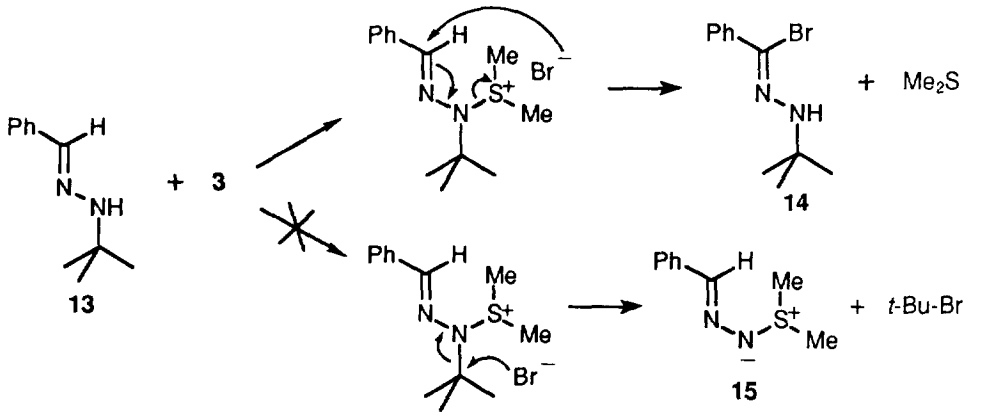
Scheme 4

loss of dimethylsulfoxide to give the corresponding cation. This stable cation undergoes attack by the counteranion, Cl^-, to give alkyl halide. Analogously, we propose the formation of a benzylic cation **10**, which may be very stable because of the additional feature, the presence of adjacent N atom. This cation can undergo nucleophilic attack by the counteranion, Cl^-, to give phenylazobenzyl chloride, which can tautomerise to *N*-phenylhydrazonyl chloride **4a**.

We found that even hydrazones of aliphatic aldehydes can be converted to hydrazonyl halides (Table 2). In these cases formation of a cation is unlikely, because it would not be stable. This indicates that formation of a stable cation is not a prerequisite, and an alternative mechanism involving direct attack of Cl^- on the carbonyl carbon, followed by loss of Me_2S, in a concerted fashion might well be operative. It should be noted, however, that even in hydrazone **6a**, allylic type resonance is possible.

At the outset, we expected that the conditions of the reaction would influence the outcome significantly. Intermediate **9**, under neutral conditions is expected to undergo nucleophilic attack by Cl^-. However under basic conditions, abstraction of the H in SCH_3, in intermediate **9** might be more favourable and ylide **11** might form instead of halide **4a**. This ylide can undergo Sommlett–Hauser type rearrangement in two ways, depicted as "path a" and "path b" in Scheme 4. Thus, when we performed the reaction in the presence of triethylamine (varying amounts), we obtained both the products **12a** and **12b**, resulting from rearrangement, in trace amounts; hydrazonyl halide **4a** was formed only in 78% yield. This implies that nucleophilic attack is much faster than ylide-formation. All side reactions are thus suppressed and hydrazonyl halides are the major products formed.

Furthermore, we studied *t*-butyl hydrazone **13**.[17] It is an interesting case in that it possesses two sites where the counteranion can attack. In addition to attack at the carbonyl carbon, there exists a possibility of attack at the tertiary carbon of the *t*-Bu group, which would give the ylide **15**. We intended to see which one was more likely and subjected it to the typical



Scheme 5

reaction conditions. The result was somewhat surprising; only hydrazonyl bromide **14** was formed. Attack at the carbonyl carbon completely overwhelmed that at the tertiary carbon center. This feature is particularly interesting as it introduces an element of regioselectivity in the method (Scheme 5).

Conclusion.—We feel to have herein demonstrated a mild and efficient method for the synthesis of hydrazonyl halides from easily available precursors, hydrazones. The reagent required, the NCS/NBS–Me_2S complex (Corey–Kim reagent), is inexpensive and can be conveniently prepared *in situ*. Furthermore, the reaction times are short, and the procedure is simple.

Experimental

Reactions were carried out in oven-dried glassware (130 °C) under an atmosphere of nitrogen. Dichloromethane was freshly distilled from P_2O_5. Ethyl acetate and hexane were dried and distilled over CaH_2. Melting points were obtained with a Büchi 510 apparatus and are uncorrected. Purification was done by column chromatography by use of EM Reagents Silica Gel 60 (particle size 0.063–0.200 mm, 70–230 mesh ASTM). Infrared (IR) spectra were recorded on a Perkin–Elmer FT 1600 spectrophotometer. Proton NMR spectra were recorded on a Varian XL-200, 200 MHz spectrometer in chloroform-*d* as solvent and tetramethylsilane as an internal standard. Chemical shifts are given in ppm and coupling constant (*J*) in Hz. Low-resolution mass spectra were obtained by means of HP 59970 workstation formed by HP-5890 gas chromatograph equipped with methylsilicone capillary and HP-5970 mass detector.

N-*Arylhydrazonyl halides* **4** *and* **5**: *General Procedure.*—*N*-Halosuccinimide (10 mmol) was dissolved in CH_2Cl_2 (70 mL) under an atmosphere of N_2. Dimethyl sulfide (1.12 g, 18 mmol) was added at 0 °C with stirring. A white precipitate that appeared almost immediately was allowed to stir for 5 min at 0 °C. The reaction mixture was cooled to – 40 °C and a solution of hydrazone[21] **1** (6 mmol) in CH_2Cl_2 (10 mL) was added to it. The progress of the reaction was monitored by TLC analysis (30–140 min). The reaction mixture was allowed to warm to 0 °C over 1 h and was quenched with cold water. The contents were extracted with CH_2Cl_2 (40 mL), washed with water (2 × 40 mL) and brine (40 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure to give **4** or **5** which were purified by column chromatography over silica gel using ethyl acetate and hexane as eluent or by crystallisation from CH_2Cl_2–pet ether. The spectroscopic and physical data were consistent with those reported (see Table 1).

4a: ^{1}H NMR δ 6.96 (1 H, t, ArH), 7.14–7.48 (7 H, m, ArH), 7.95 (2 H, d, ArH), 8.05 (1 H, br, NH); MS *m*/*z* 232, 230.

N-*Phenylalkanehydrazonyl halides* **7**, **8** *and* **14**.—*N*-Halosuccinimide (2.5 mmol) was dissolved in CH_2Cl_2 (30 mL) under an atmosphere of N_2. Dimethyl sulfide (0.285 g, 4.5 mmol) was added at 0 °C with stirring. The reaction mixture was cooled to – 60 °C and a solution of hydrazone **6** or **13** (1.45 mmol) in CH_2Cl_2 (8 mL) was added to it. The reaction mixture was stirred at that

temperature for 2 hrs. The temperature was then raised to – 30 °C. The progress of the reaction was monitored by TLC analysis (30–50 min). The reaction mixture was allowed to warm to 0 °C over 1 h and was quenched with cold water. It was worked-up in a similar manner as discussed above, to give **7**, **8** or **14** which were purified by column chromatography over silica gel using ethyl acetate and hexane as eluent or by crystallisation from CH_2Cl_2–pet ether. The spectroscopic and physical data were consistent with those reported (see Table 2). Compounds **7b**, **8** and **14** were difficult to purify because of their instability on silica gel and at higher temperature, hence we were not able to obtain accurate elemental analysis.

7a: ^{1}H NMR δ 1.25 (3 H, t, *J* = 7 Hz, CH_3), 2.65 (2 H, q, *J* = 7 Hz, CH_2), 6.61–7.33 (5 H, m, ArH), 7.52 (1 H, br s, NH); IR ($CHCl_3$) 3293, 1604, 1506 cm^{-1}; MS *m*/*z* 184, 182.

7b: ^{1}H NMR δ 4.20 (2H, s CH_2), 6.86–7.78 (10 H, m, ArH), 7.91 (1 H, br s, NH); IR ($CHCl_3$) 3298, 1602, 1501 cm^{-1}; MS *m*/*z* 246, 244.

7c: ^{1}H NMR δ 2.61 (2 H, t, *J* = 7 Hz, CH_2), 3.17 (2 H, t, *J* = 7 Hz, CH_2), 6.59–7.83 (11 H, m, NH, ArH); IR ($CHCl_3$) 3342, 1604, 1506 cm^{-1}; MS *m*/*z* 260, 258.

7d: ^{1}H NMR δ 6.76–7.57 (12 H, m), 7.93 (1 H, br s, NH); IR ($CHCl_3$) 3320, 1604, 1505 cm^{-1}; MS *m*/*z* 258, 256.

8a: ^{1}H NMR δ 1.26 (3 H, t, *J* = 7 Hz, CH_3), 2.75 (2 H, q, *J* = 7 Hz, CH_2), 6.92–7.36 (5 H, m, ArH), 7.54 (1 H, br s, NH); IR ($CHCl_3$) 3293, 1604, 1506 cm^{-1}; MS *m*/*z* 228, 226.

8b: ^{1}H NMR δ 4.21 (2H, s CH_2), 7.03–7.79 (10 H, m, ArH), 7.93 (1 H, br s, NH); IR ($CHCl_3$) 3311, 1600, 1501 cm^{-1}; MS *m*/*z* 290, 288.

8c: ^{1}H NMR δ 2.63 (2 H, t, *J* = 7 Hz, CH_2), 3.20 (2 H, t, *J* = 7 Hz, CH_2), 6.62–7.84 (11 H, m, NH, ArH); IR ($CHCl_3$) 3337, 1602, 1503 cm^{-1}; MS *m*/*z* 304, 302.

14: ^{1}H NMR δ 1.33 (9 H, s, 3 X CH_3), 5.64 (1 H, br s, NH), 7.38–7.93 (5 H, m, ArH); IR ($CHCl_3$) 3298, 1608, 1505 cm^{-1}; MS *m*/*z* 256, 254.

Reaction of Hydrazone ***1a*** *with* **2** *in the presence of triethyl amine.*—*N*-Chlorosuccinimide (0.133 g, 1.0 mmol) was dissolved in CH_2Cl_2 (30 mL) under an atmosphere of N_2. Dimethyl sulfide (0.112 g, 1.8 mmol) was added at 0 °C with stirring. The reaction mixture was cooled to – 40 °C and a solution of hydrazone **1a** (0.118 g, 0.6 mmol) and Et_3N (0.105 g, 1.1 mmol) in CH_2Cl_2 (10 mL) was added to it. The progress of the reaction was monitored by TLC analysis (30 min). The reaction mixture was allowed to warm to 0 °C over 1 h and was quenched with cold water. It was worked-up in a similar manner as discussed above, to give **4a** (78%), along with **12a** and **12b** (in trace amount). The spectroscopic and physical data are consistent with those reported (see Table 1).

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