Observations on the reaction of hydrazones with iodine: interception of the diazo intermediates†‡

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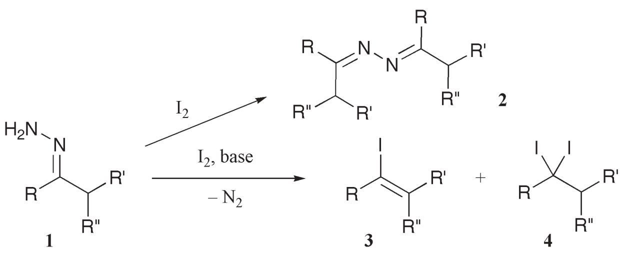
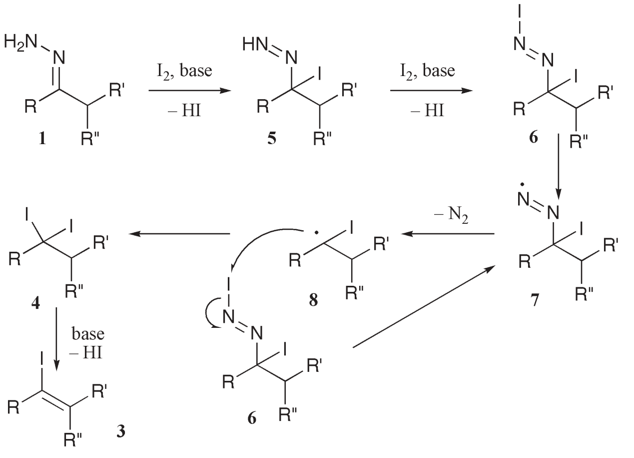
The reaction of hydrazones with iodine/base leads to diazo intermediates that can be trapped by an internal alkene or alkyne.

The reaction of hydrazones **1** with iodine was reported in 1911 by Wieland and Roseeu to give azines **2**.[1] Later, Barton and co-workers confirmed the formation of azines in the absence of base but showed that a combination of iodine and triethylamine provided, in addition to the azine, a vinyl iodide **3** and sometimes variable amounts of *geminal* diiodide **4**, as indicated in Scheme 1.[2a] The yield of the vinyl iodide was later improved by using a stronger amidine or guanidine base[2b,d] and by modifying the order of addition of the reagents to avoid azine formation. It was also found that replacing the iodine with an arylselenyl halide allows the synthesis of the corresponding vinyl selenides.[2c,d] This reaction has found many applications,[3] since vinyl halides play a central role in a number of transition metal induced couplings, but its mechanism has remained somewhat unclear. A radical mechanism was proposed for the formation of azine and an ionic mechanism for the pathway leading to the vinyl iodide. In the present Communication we describe the capture of a diazo intermediate, which not only sheds light on the reaction pathway but also opens up some interesting synthetic possibilities.

The question we set out to answer was whether the loss of nitrogen occurs by an ionic or a radical mechanism. As outlined in Scheme 2, a chain reaction can be postulated involving a diazenyl radical and an iodine atom transfer step. Thus, two successive iodinations would lead to azodiiodide **6** *via* monoiodide **5**. This intermediate contains a weak N–I bond that can spontaneously rupture to give diazenyl radical **7**, which should rapidly lose molecular nitrogen to give resonance stabilised carbon-centred radical **8**. Iodine atom exchange with azodiiodide **6** would then furnish concomitantly diiodide **4** and diazenyl radical **7**, the latter serving to propagate the chain. Base induced elimination of hydrogen iodide would finally deliver the vinyl iodide.

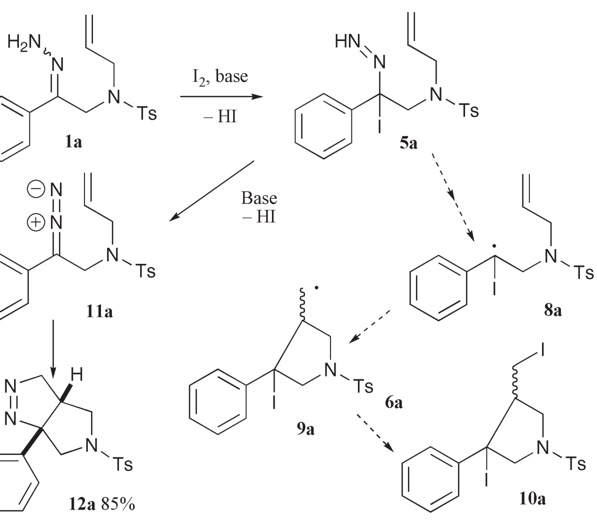


Scheme 1 Vinyl iodides and *gem*-diiodides from hydrazones.



Scheme 2 Possible mechanism for the formation of vinyl iodides.

If such a mechanism is indeed operating, then it should be possible to capture carbon-centred radical **8** by an internal olefin as shown in Scheme 3. Starting from hydrazone **1a**, such a step would lead to a new carbon radical **9a**, which could then exchange an iodine atom from its corresponding azodiiodide precursor **6a** (not drawn) to give diiodopyrrolidine **10a**.



Scheme 3 Formation and capture of a diazo intermediate.

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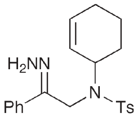
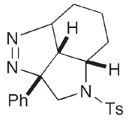
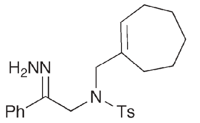
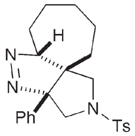
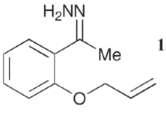
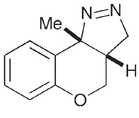
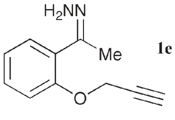
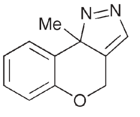
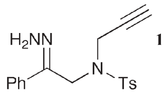
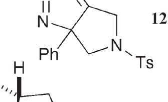
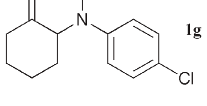
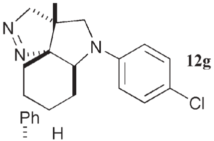
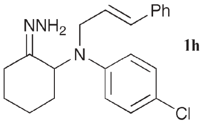
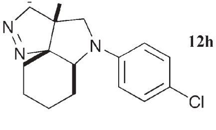
‡ This article is dedicated with respect and affection to the memory of Professor Pierre Potier.

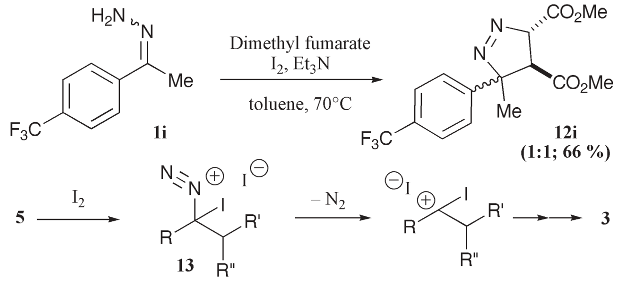
Hydrazone **1a** was easily made from the corresponding ketone, itself prepared from phenacyl bromide and *N*-allyltoluenesulfonamide using standard chemistry. When **1a** was treated with iodine and DBU in toluene at room temperature under the typical conditions for the Barton reaction, none of the expected diiodopyrrolidine **10a** was observed.§ Nor did the reaction produce the normal vinyl iodide **3a** (not drawn). Instead, cyclic diazo derivative **12a** was obtained in high yield. Clearly, radicals are not involved in the process, which takes place in fact by way of diazo intermediate **11a**. From a synthetic standpoint, this experiment highlights the possibility of intercepting the diazo intermediate *before its further reaction with iodine to give vinyl iodide* ***3*** *occurs*.[4]

The generality of this extension of the Barton transformation is illustrated by the examples in Table 1. Complex structures, all containing a newly created quaternary centre, can thus be rapidly assembled in uniformly high yields. Five- and six-membered rings adjacent to the pyrazoline unit are readily formed from both alkenes and alkynes. The reaction is successful with either aromatic or aliphatic ketones. In the latter case we encountered, not surprisingly, a competing formation of azines during the synthesis of the starting hydrazones. This complication was solved by using a slight modification of the conditions described by Nenajdenko *et al.*,[5] consisting of adding a few drops of acetic acid to a solution of the ketone and hydrazine in DMSO. Finally, triethylamine proved to be as efficient as DBU. The possibility of using a much milder base should expand significantly the tolerance of this method to many useful functional groups.§

Table 1 Formation and capture of diazo intermediates

	**1b**		**12b** 67%
	**1c**		**12c** 100%
	**1d**		**12d** 76%
	**1e**		**12e** 60%
	**1f**		**12f** 60%
	**1g**		**12g** 79%[a]
	**1h**		**12h** 100%[a]

[a] Triethylamine was used in these cases.



Scheme 4 Intermolecular capture and mechanism.

Not unexpectedly, intermolecular capture of the diazo intermediate proceeded less effectively and had to be done under modified experimental conditions favouring a bimolecular process (increased concentration and excess of the olefin trap). Thus, when a solution of iodine in toluene was added slowly to a hot (60 °C) toluene solution of hydrazone **1i**, triethylamine, and a 5-fold excess of dimethyl fumarate, the logical cycloadduct **12i** was formed in 66% yield as a 1 : 1 mixture of diastereoisomers (Scheme 4).§

In the light of the above observations, it appears that the loss of nitrogen *en route* to the vinyl iodides **3** occurs ionically *via* the diazonium salt, as originally proposed by Barton[2e] (Scheme 4). Nevertheless, the oxidation of diazo intermediate **5** into diazonium salt **13** is slow enough to allow a useful interception of the former.

Notes and references

§ Typical experimental procedures: To a solution of the hydrazone (1 mmol) and DBU (4 mmol) or triethylamine (4 mmol) in toluene (8–10 mL) was added dropwise, under nitrogen, a solution of iodine (1.5 mmol) in toluene (8–10 mL) until the iodine coloration persisted. After complete consumption of the starting material (monitored by TLC) the reaction mixture was extracted with ethyl acetate and washed with an aqueous solution of HCl (1 N), $Na_2S_2O_3$ and brine. The combined organic layers were dried (Na_2SO_4), filtered and evaporated under reduced pressure to give the diazo compound, which was purified by chromatography on a silica gel column or by recrystallisation (for spectral data for cycloaddition compounds, see supplementary information).

1 H. Wieland and A. Roseeu, *Justus Liebigs Ann. Chem.*, 1911, **381**, 232.

2 (*a*) D. H. R. Barton, R. E. O'Brien and S. Sternhell, *J. Chem. Soc.*, 1962, 470; (*b*) A. Pross and S. Sternhell, *Aust. J. Chem.*, 1970, **23**, 989; (*c*) D. H. R. Barton, G. Bashiardes and J.-L. Fourey, *Tetrahedron Lett.*, 1983, **24**, 1605; (*d*) D. H. R. Barton, G. Bashiardes and J.-L. Fourey, *Tetrahedron Lett.*, 1984, **25**, 1287; (*e*) D. H. R. Barton, G. Bashiardes and J.-L. Fourey, *Tetrahedron*, 1988, **44**, 147.

3 For some recent examples, see: (*a*) H. Kawada, M. Iwamoto, M. Utsugi, M. Miyano and M. Nakada, *Org. Lett.*, 2004, **6**, 4491; (*b*) T. P. Brady, S. H. Kim, K. Wen and E. A. Theodorakis, *Angew. Chem., Int. Ed.*, 2004, **43**, 739; (*c*) A. S. Kende, W. P. Deng, M. Zhong and X.-C. Guo, *Org. Lett.*, 2003, **5**, 1785; (*d*) D. R. Williams and R. W. Heidebrecht, *J. Am. Chem. Soc.*, 2003, **125**, 1843; (*e*) K. Ogawa, T. Okazaki and T. Kinoshita, *J. Org. Chem.*, 2003, **68**, 1579; (*f*) O. Roy, G. Pattenden, D. C. Pride and C. Wilson, *Tetrahedron*, 2003, **59**, 5115; (*g*) M. Helliwell, E. J. Thomas and L. A. Townsend, *J. Chem. Soc., Perkin Trans. 1*, 2002, 1286; (*h*) B. Vaz, R. Alvarez and A. R. de Lera, *J. Org. Chem.*, 2002, **67**, 5040; (*i*) S. F. Martin, C. Limherakis, L. E. Burgess and M. Hartmann, *Tetrahedron*, 1999, **55**, 3561.

4 M. Regitz and G. Maas, *Diazo Compounds: Properties and Synthesis*, Academic Press: Orlando, 1986. For a review of intramolecular cycloadditions of diazo derivatives, see: P. A. Wade, in *Comprehensive Organic Synthesis*; B. M. Trost, I. Fleming, Eds; Pergamon Press: Oxford, 1991; Vol. 4, pp. 1151–1157. For recent examples, see: G. Maas, V. Gettwert, F. Krebs and G. Schmidtberg, *Chem.-Eur. J.*, 2000, **6**, 1646; V. K. Aggarwal, J. de Vicente and R. V. Bonnert, *J. Org. Chem.*, 2003, **68**, 5381.

5 V. N. Korotchenko, A. V. Shastin, V. G. Nenajdenko and E. S. Balenkova, *Org. Biomol. Chem.*, 2003, **1**, 1906.