Trichloroacetylhydrazones: new highly reactive alkylating agents

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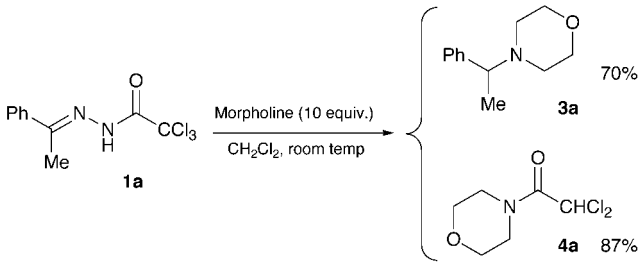
The behavior of trichloroacylhydrazones as new highly reactive alkylating agents is disclosed; various secondary amines are alkylated within a few minutes at room temperature, and similar alkylating reductions were found with malonates.

Hydrazones are associated with a wealth of well-known reactions, such as the Wolf Kishner[1] and Shapiro[2] reactions and the Eischenmoser rearrangement.[3] In most of these fascinating reactions, loss of nitrogen is the driving force of the observed modifications. We recently reported a puzzling reaction of a class of poorly studied hydrazones, trichloroacetylhydrazones; when a number aldehyde derivatives were treated with K_2CO_3, clean conversion to 1,3,4-oxadiazoles was observed.[4] In order to have a better understanding of the behavior of these compounds, we decided to treat them in a different basic medium.

When hydrazone **1a** was treated with a large excess of morpholine in CH_2Cl_2, fast evolution of nitrogen was observed at room temperature along with the unexpected formation of the new alkylated amines **3a** and the dichloroacylamide **4a** (Scheme 1) as the only isolable compounds. The overall process from the carbonyl starting material is a reductive alkylation, as observed in the Leuckart reaction.[5] The reaction seems to be general, with ketone and aldehyde hydrazones **1** giving in a similar fashion the new alkylated amines **3** when treated with a large excess of amine **2** (Table 1). In most instances, the reaction was very clean and analysis of the crude product revealed that amines **3** and dichloroamides **4** were the only formed products; the pure amines **3** were most efficiently recovered through acid-base extraction and removal of the volatile secondary amine by evaporation. The poor isolated yield observed for **3f** was probably due to losses during evaporation of the morpholine. However, with aromatic ketones different behavior was observed when the morpholine was replaced by Et_2NH (or $Pr^i{}_2NH$); instead of the expected reduced compounds, formal oxidation of the ketone to the new α-amino hydrazone **5a** (or **5b**) occurred (Table 1).

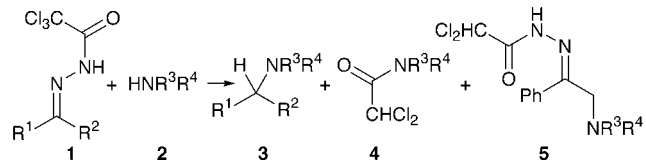


Scheme 1

Under the same conditions, primary amines also gave a fast reaction with trichloroacylhydrazones, but no alkylation compounds could be recovered from the complex product mixtures.

The use of a large excess of secondary amine could be a serious drawback for the application of this chemistry to other nucleophiles. Even if the amount of amine could be lowered, at least 1 equiv. was always lost as a trap for the dichloroacyl group. A solution to this problem was eventually given by the observation that trichloroacylhydrazones were rather unreactive in ethanolic sodium ethanolate. When hydrazone **1e** was left to react in a EtONa (4 equiv.) solution in EtOH, no change was observed after 4 h at room temperature; when the same solution was refluxed for 5 h the new oxadiazole **10a** was formed in 48% yield (Scheme 2). This behavior was similar for various hydrazones tested. We then added hydrazone **1f** to a EtONa (1.2 equiv.) solution in absolute EtOH, observed after a quarter of an hour the absence of reaction, and then added to this mixture diethyl malonate (1.2 equiv.); the evolution of nitrogen was soon observed. The reaction was left at room temperature for one day, after which the usual workup gave the alkylated

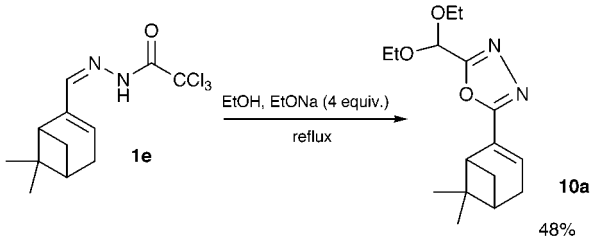
Table 1 Isolated compounds after aminolysis of hydrazones **1**



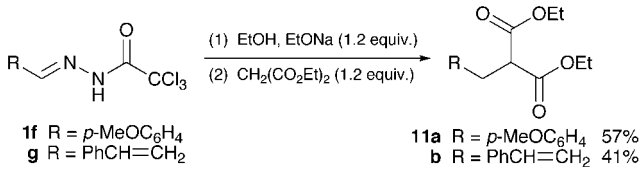
1 2 3 4 5

Hydrazone[a]			Amine			Product (% yield[b])		
1	R^1	R^2	**2**	R^3	R^4	**3**	**4**	**5**
1a	Ph	Me	**2a**	$-(CH_2)_2O(CH_2)_2-$		**3a** (70)	**4a** (87)	—
1a	Ph	Me	**2b**	$-(CH_2)_5-$		**3b** (68)	—	—
1b	$-(CH_2)_2CH{=}CHCH_2-$		**2a**	$-(CH_2)_2O(CH_2)_2-$		**3c** (89)	—	—
1b	$-(CH_2)_2CH{=}CHCH_2-$		**2c**	Et	Et	**3d** (98)	—	—
1c	Ph	H	**2a**	$-(CH_2)_2O(CH_2)_2-$		**3e** (71)	—	—
1d	$-(CH_2)_4-$		**2a**	$-(CH_2)_2O(CH_2)_2-$		**3f** (42)	—	—
1a	Ph	Me	**2c**	Et	Et	—	—	**5a** (57)
1a	Ph	Me	**2d**	Pr^i	Pr^i	—	—	**5b** (67)

[a] Yields from ketones: **1a** (64%), **1b** (50%), **1c** (75%), **1d** (65%). [b] Isolated yields.



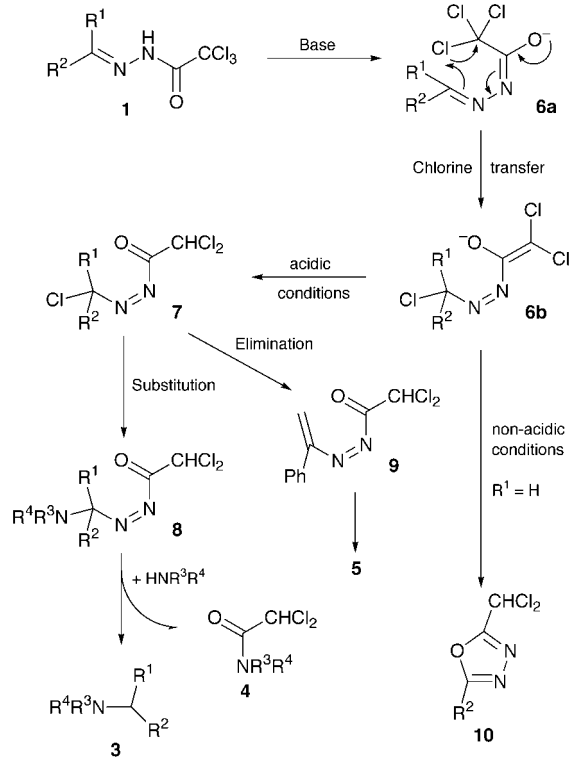
Scheme 2



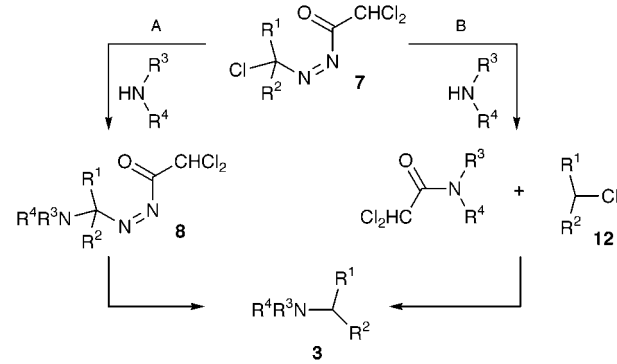
Scheme 3

malonate **11a** in 57% yield (Scheme 3). The same reaction with cinnamaldehyde hydrazone **1g** gave the new malonate **11b** in a poor 41% yield.

A reasonable mechanism for all these results is depicted in Scheme 4. The main assumption lies in a 1,5 chlorine migration from the anion. Such a migration has never been reported before but could be relevant in the results described by Yiannios *et al.* in 1968.[6] In our case the evolution of the resulting anion **6** depends on the nature of the substituted hydrazones (R = alkyl, aryl, H) and the basic conditions used in the reaction. When reprotonation of **6** is not possible (K_2CO_3, dioxane), a cyclisation to oxadiazole **10** is observed for aldehyde hydrazones giving reactive chlorides (R^1 = H, R^2 = aryl, alkenyl). When the medium is acidic enough (excess of amine and the presence of ammonium chloride salts), protonation of **6** to the α-chloroazo intermediate **7** may lead to the products through subsequent substitution and elimination reactions. With substrates sensitive to base elimination different behavior is observed: elimination of HCl from **7** (R^1 = Me, R^2 = Ph) leads



Scheme 4



Scheme 5

to azoalkenes **9** (Scheme 4) whose chemistry has been fully explored in Michael type additions or cycloadditions with nucleophiles;[7] in our case, their reaction with Et_2NH (or Pr^i_2NH) in excess gives the observed amino hydrazone **5a** (or **5b**). This elimination is best observed with poorly nucleophilic amines; indeed highest yields were obtained with Pr^i_2NH whereas the more nucleophilic morpholine led to tertiary amine **3a**.

The acidic requirements of this reaction are stressed by the experiments conducted in EtOH. The mixture of EtONa in EtOH is not acidic enough and no reaction is observed at room temperature, however the reaction starts as soon as the slightly acidic malonate is added in the mixture.[8]

The intermediacy of chloride **12** (Scheme 5, path A) was discarded in view of the sluggish reaction observed between morpholine and chlorocyclopentane in CH_2Cl_2. After 4 h at room temperature, no formation of amine **3f** was observed; hydrazone **1** under the same conditions gives amine **3f** within 10 min, revealing the highly electrophilic properties of the intermediate involved.

Trichloroacylhydrazones certainly deserve further study to fully understand the mechanism of these reactions and exploit their full potential, yet these reductive alkylations at room temperature are most noteworthy. Whatever the structure of the active alkylating agent generated under weakly basic conditions, it is much more reactive than the related chloride and can be generated from stable starting materials with weak bases. Besides their synthetic potential underlined here trichloroacylhydrazones could find useful applications in the biological field as masked alkylating species activated after interaction with a basic site of an enzyme receptor.

Notes and references

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7 O. A. Attanasi and P. Filippone, *Synlett*, 1997, 1128.

8 Alternative intermediates such as oxadiazoles and diazo compounds can be easily proposed in the alkylation process; several analogues of these compounds have been isolated during a study on the basic treatment of the related monochloroacylhydrazones: E. C. Taylor, N. F. Haley and R. J. Clemens, *J. Am. Chem. Soc.*, 1981, **103**, 7743. The experiments conducted in EtOH are however difficult to explain with these intermediates.

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