Pergamon

Tetrahedron Letters 39 (1998) 6885–6888

TETRAHEDRON
LETTERS

Trichloroacetic acid hydrazones I: New formation of 1,3,4-oxadiazoles from aldehydes

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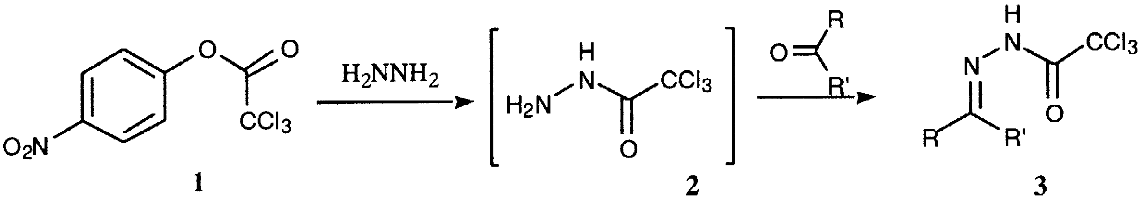
Received 10 June 1998; accepted 15 July 1998

Abstract : Trichloroacetic acid hydrazones, prepared from the condensation of carbonyl derivatives with trichloroacetic acid hydrazide, display interesting chemical behaviour in the presence of a base. Aromatic and α,β-unsaturated aldehyde hydrazones in particular are easily transformed into 1,3,4 oxadiazoles derivatives. This original reaction represents a new formal oxydation of aldehydes into acid derivatives in non oxydative conditions.

Hydrazones display fascinating chemical behaviour giving many useful reactions according to the substituent on the terminal nitrogen. Free hydrazones have been extensively used in the Wolff-Kishner reaction[1] whereas sulfonyl hydrazones lead to diazo compounds[2], alkenes[3] or alkynes[4]. Radical chemistry of hydrazones have also been fruitfully exploited in the last ten years[5]. Acyl hydrazones share with the other members of this family their easy formation from acyl hydrazine and aldehyde or ketone; hundreds of these hydrazone derivatives have been reported in the litterature. Surprisingly only few reports on trichloroacetic acid hydrazones are available[6,7,8,9].

The few studies reported on chloroacetic acid hydrazone must be associated with the instability of chloroacetic acid hydrazides wich have only been isolated in their chlorhydrate form[7]. Indeed, fast elimination of nitrogen is often observed when preparing trichlorohydrazide **2** without proper experimental conditions[7]. Best conditions for preparation of hydrazones[7] **3** involve the intermediate formation of 4-nitrophenol trichloroacetate **1**, followed by treatment with hydrazine[10] and *in situ* trapping with a carbonyl derivative[11] (Scheme 1):

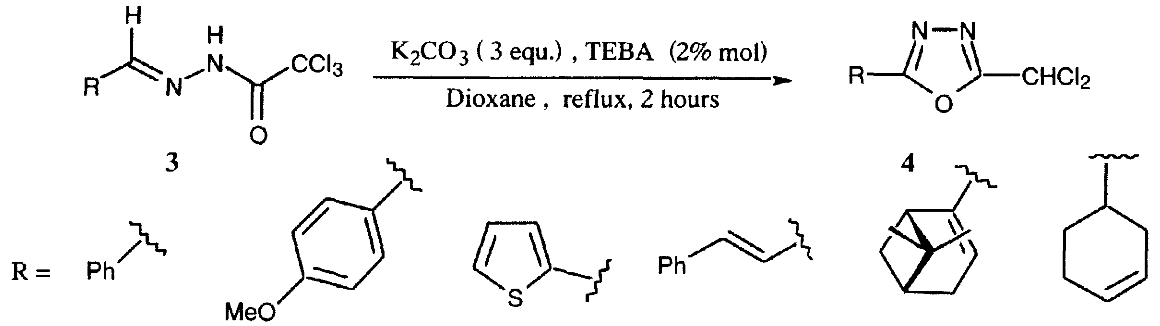


1 **2** **3**

Scheme 1

0040-4039/98/$ - see front matter
PII: S0040-4039(98)01503-2

When treating various aldehyde hydrazones **3** with potassium carbonate under phase transfer conditions, we observed an unprecedented rearrangement giving in a single step new oxadiazoles **4** (Scheme 2). This remarkable transformation involves formal oxidation of the aldehyde into an acid and reduction of the trichloromethyl moiety into a dichloromethyl group.

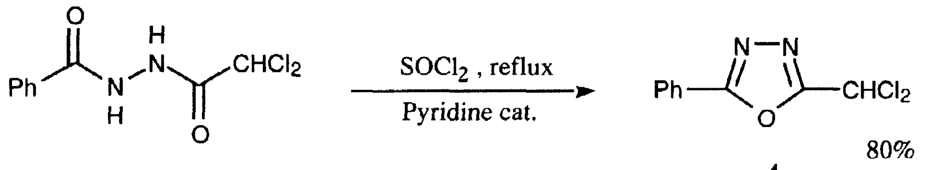


3a,4a	**3b,4b**	**3c,4c**	**3d,4d**	**3e,4e**	**3f,4f**
72%	79 %	52 %	78 %	80 %	0 %

Scheme 2

The reaction gives good yields with aromatic aldehydes as well as α,β-unsatured aldehydes but several attempts with aliphatic aldehydes didn't meet with success **3f**. In the same conditions, the related hydrazone of acetophenone gave a complex mixture of compounds.

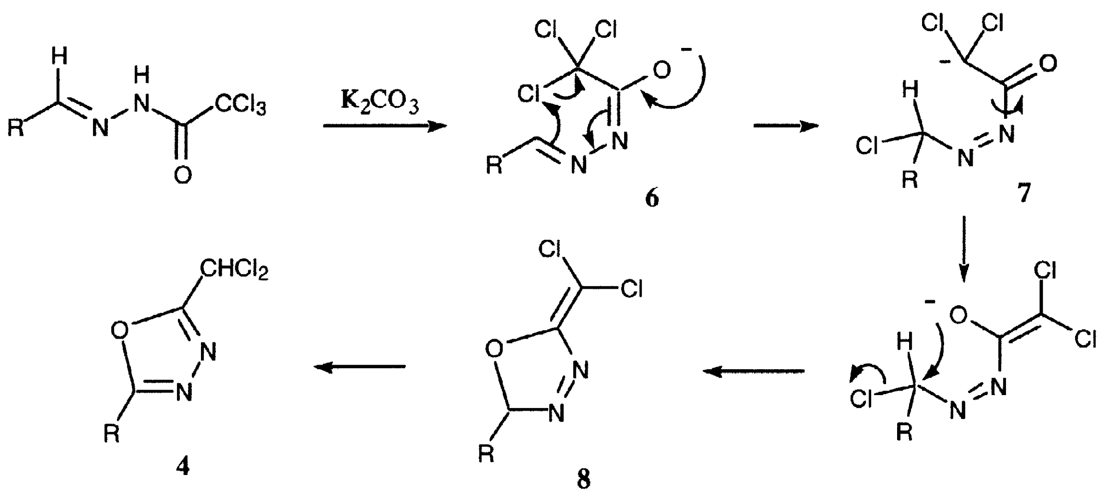
The identity of the formed oxadiazole has been checked by a more conventionnal preparation of oxadiazole **4a** from diacylhydrazide **5** and thionyl chloride (Scheme 3).



5 **4a**

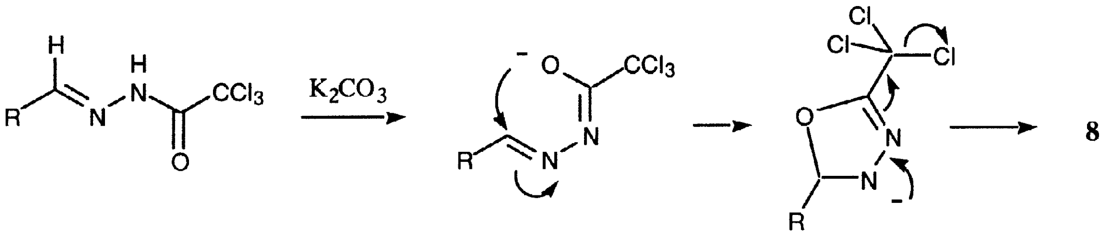
Scheme 3

Our conversion which enables the formation of oxadiazoles under non acidic conditions is most noteworthy in revealing a new chemical behaviour of acyl hydrazones. The mechanism of this reaction probably involves a chlorine transfer from the deprotonated hydrazone **6** (Scheme 4); following cyclisation and prototropy could afford oxadiazole **4**.



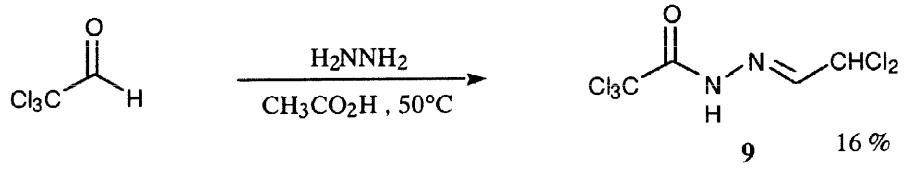
Scheme 4

The transformation of **6** into **7** is a formal [1,5] sigmatropic rearrangment assisted by the charged oxygen atom. An alternative mechanism that doesn't rely on chlorine migration may be proposed for this reaction (Scheme 5).



Scheme 5

This mechanism was rejected in view of the reactivity pattern observed: oxadiazole formation was only effective for starting materials giving intermediates **7** with activated chlorine in allylic or benzylic positions. This activation ensures fast cyclisation to intermediate **8**. Furthermore, a related reaction has been observed when condensing chloral with hydrazine; under anhydrous conditions, the new acyl hydrazone **9** is formed in poor yield (Scheme 6)[6]. As in our study, one can notice in structure **9**, the similar balance in oxydation and reduction of the two chemical moieties tethered to nitrogens. The reaction mechanism for this latter reaction is clearly closer to one depicted in scheme 4.



Scheme 6

The potential of this chlorine transfer certainly deserves further study and new results from this chemistry as well as synthetic applications of chloroacyl hydrazones will be reported soon from our research group.

References and notes

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10 Hydrazine hydrate can be used instead of anhydrous hydrazine giving slightly lower yields
11 The separation of nitrophenol and the expected hydrazone might be troublesome (similar Rf). In most cases studied, the aldehyde hydrazone is recovered from the mixture after addition of ether and precipitation. Without precipitation, extractions of the mixture with water saturated with sodium bicarbonate removes most nitrophenol. Other possible synthesis relies on the intermediate separation of **2** (in its chlorhydrate form) followed by its reaction with the carbonyl compounds and sodium hydrogencarbonate in dichloromethane.