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# Thiophenol Promoted Radical Cyclisation of Hydrazones and Oxime Ethers

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**Abstract** : Thiophenol radical induced cyclisation of N-dimethyltriazolyl imines is reported. Ethylenic but also acetylenic tethered hydrazones are cyclised to cycloalkyl hydrazine under smooth conditions. A comparative study with oxime ethers is described.

In the last two decades, radical cyclisation has emerged as a powerful tool in organic chemistry[1]. The synthetic potential offered by the now classical ω-alkenyl radical cyclisations has been furthermore increased by the developpement of radical cyclisation on multiple bonds containing heteroatoms. Fast 5-and 6-exo-trig-cyclisation on oxime ethers has found, for instance, application in sugar chemistry[2], whereas the interest of radical cyclisation of hydrazones has been highlighted in the studies of Kim[3] and of Fallis[4] .

As part of a research program on the radical chemistry of N-benzotriazolyl imines[5], we became interested in the behavior of these hydrazones towards radicals. The impressive rate constant for 5- and 6-exo cyclisations of N,N-diphenylhydrazones ($10^{8}\,S^{-1}$) reported by Fallis led us to investigate the potential of sulfur derivatives as hydrogen transfer agent in the radical cyclisation. Indeed most results on hydrazone cyclisations have been obtained with tin hydride derivatives, which are troublesome on cost, toxicity and purification matters. Thiols are known to add easily on alkene and alkyne. The application of thiyl radical chemistry to the cyclisation of dienes[6], enynes[7] and diynes[8] systems has often been impeded by a fast reduction of the β-sulfur alkyl radical prior cyclisation[9]. In the case of ω-acetylenic hydrazone, we expected that radical addition of thiyl radical to the alkyne could be followed by a fast cyclisation without reduction of the intermediate vinylic radical. In order to test these assumptions, we prepared, according to usual synthetic procedure, 5-substitued allyl and acetylenic hydrazones, and let them react with thiols in radical conditions in order to afford cycloalkyl substitued hydrazines.

When a cyclohexane solution of hydrazone (**a**) (c = $10^{-1}$M) is thus heated for a few hours under reflux with thiophenol (1,2 eq.) and AIBN (0,1 eq.), the hydrazine (**b**) is recovered after evaporation of the solvent and

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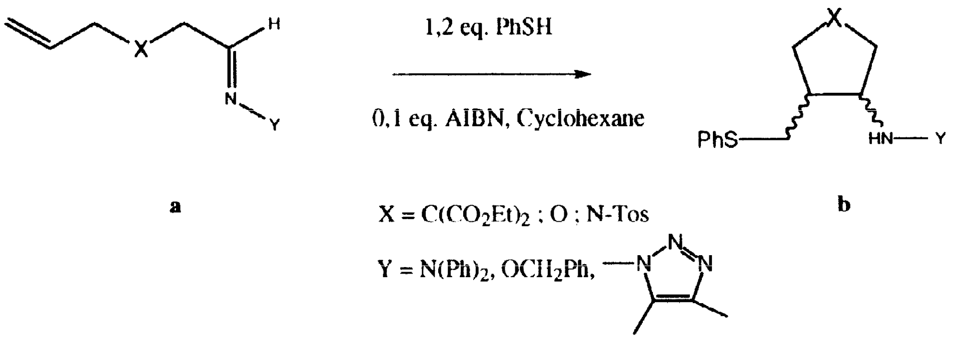
chromatography (scheme 1, Table 1). A mixture of diastereomers is obtained, the cis isomer being the major as shown by NMR experiment.

The first results obtained with the ω-alkenyl diphenyl hydrazone **5a** and the ω-alkynyl diphenyl hydrazone **13a** were successful, notwithstanding purification problems in the preparation of the starting hydrazone. We therefore examine the reactivity of other hydrazones and oxime ethers, in the same reaction conditions.

**Scheme 1**



The results summarized in Table 1 show that cyclisation occur either on ethylenic or acetylenic hydrazones, the later being faster probably due to the high reactivity of the intermediate vinylic radical. Knowing that vinylic radicals and thiophenols react by a fast $S_H2$ process, it is noteworthy that no trace of uncyclised product could be detected under these conditions. 6-exo cyclisation on the other hand occurs with the acetylenic compound **11a**, but not with the ethylenic compound **10a**. All attempts to obtain the uncyclised product in the later case failed (even with thiophenol used as solvent). The diastereoselectivity observed is similar to the one reported by Fallis et al. in their work on halodiphenylhydrazones[6].

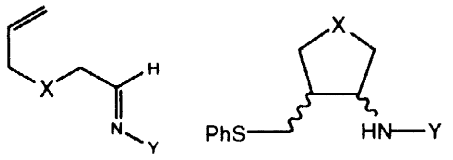
Whatever the subtituent Y, N-tosylamides derivatives (compounds **3a** to **6a**) afford in similar reaction times and yields the corresponding cyclopentyl hydrazines (compounds **3b** - **6b**). The good results obtained with the oxime ether compared to the hydrazone were rather surprising in view of the known cyclisation rate of these compounds. In the case of oxime ether, slow cyclisation could be conterbalanced by a faster hydrogen transfer in the following step. To ascertain the potential of oxime ethers in radical cyclisation, complementary experiments were conducted on compounds **2a**, **4a**, **8a**, **12a**.

The acetylenic oxime ether **8a** reacts in the same way as that previously observed with hydrazones **7a**. The intermediate vinylic radical formed reacts with the carbon of the oxime ether to afford the corresponding cyclic product without undergoing preliminary reduction. Consistent with the known reactivity of oxime ethers vs. hydrazones with radicals, we observed that 6-exo cyclisation on acetylenic hydrazones was not reproducible on acetylenic oxime ether **12a**.

Table 1 : **Radical Cyclisation of Hydrazones and Oxime Ethers**

| Substrate | Product (isolated yield) | Cis/trans Ratio | Time (hr) |
|---|---|---|---|
| **1a** | 1b (76) | 70 : 30 | 3.5 |
| **2a** | 2b(75) | 80 : 20 | >5 |
| **3a** | 3b(75) | 66:33 | 5 |
| **4a** | 4b(85) | 63:37 | 3 |
| **5a** | 5b(88) | 70:30 | 3 |
| **6a** | 6b(70) | 75:25 | 4.5 |
| **7a** | 7b(70) | < 90 : 10 | 1.5 |
| **8a** | 4b(90) | 93 : 07 | 3 |
| **9a** | 9b(69) | 50 : 50 | 6 |
| **10a** | 10b(0) | no reaction | >10 |
| **11a** | 11b(60) | 70 : 30 | 5 |
| **12a** | 12b(< 10)* |  | 5 |
| **13a** | 13b(80) | 75:25 | 5 |

* A mixture of starting material and reduction product is obtained.



**1a** : $X = C(CO_2Et)_2$, $Y = dmt$ **1b**

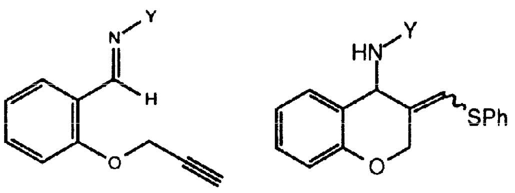
**2a** : $X = C(CO_2Et)_2$, $Y = OCH_2Ph$ **2b**

**3a** : X = N-Tos, Y = dmt **3b**

**4a** : X = N-Tos, $Y = OCH_2Ph$ **4b**

**5a**: X = N-Tos, $Y = N(Ph)_2$ **5b**

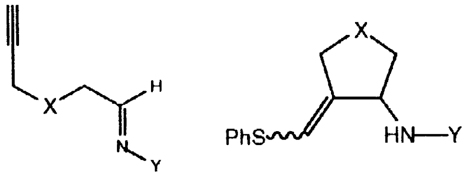
**6a** : X = N-Tos, Y = t **6b**



**11a** : Y = dmt **11b**

**12a** : $Y = OCH_2Ph$ **12b**

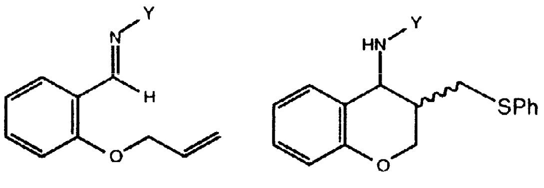
**13a** : $Y = N(Ph)_2$ **13b**



**7a** : $X = C(CO_2Et)_2$, $Y = dmt$ **7b**

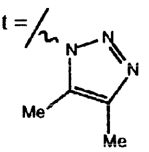
**8a** : $X = C(CO_2Et)_2$, $Y = OCH_2Ph$ **8b**

**9a** : X = O, Y = dmt **9b**

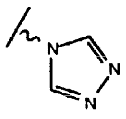


**10a** : Y = dmt **10b**

dmt =



t =



**Structures for Table 1**

This work describes the use of thiophenols in radical cyclisation of several types of hydrazones. The cyclisation of ethylenic and acetylenic systems is fast enough to be suitable for oxime ethers in 5-exo cyclisation. This reaction widens the scope of radical cyclisation on C=N bond. Further synthetic developpements are under study in our group.

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