Novel *in situ* Formation and Rearrangement of Thiohydrazonate Esters

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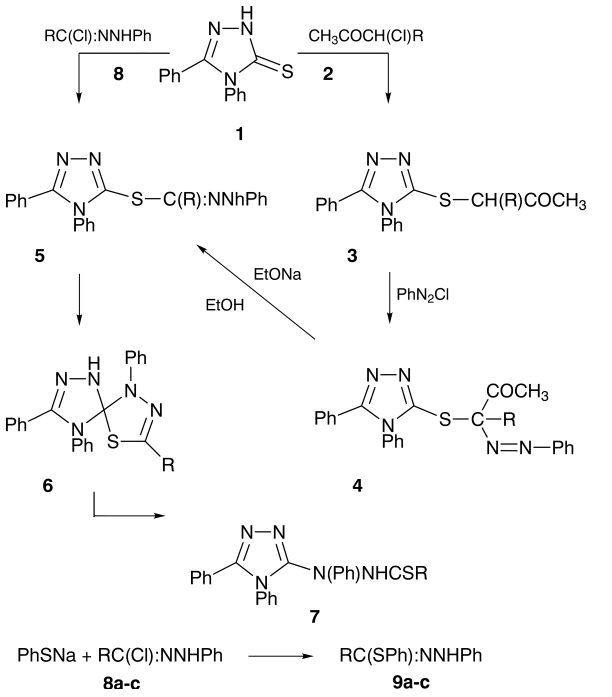
Reaction of benzenediazonium chloride with 3,4-diphenyl-1,2,4-triazol-5-ylthiomethylene compounds **3** afforded the azo coupling products **4**, which upon treatment with sodium ethoxide in ethanol yielded the title compounds that rearrange *in situ* to give the thiohydrazides **7**.

The synthesis and rearrangement of aryl hydrazonates and their thio analogs have attracted the interest of a number of research groups, including our own, because they proved useful precursors for the synthesis of *N*,*N*-disubstituted hydrazides and thiohydrazides[1,2] as well as condensed oxadiazines and thiadiazines.[2,3] As the most general synthesis of such esters is based on the use of hydrazonyl halides which are skin irritants, we have been interested in developing new syntheses in which safer precursors can be used. Herein we report the results of our attempts to apply the Japp–Klingemann reaction[4] in the synthesis of such esters. We first gave attention to coupling of benzenediazonium chloride with a series of novel active methine compounds, namely 1,2,4-triazol-5-ylthiomethylene derivatives **3** (Scheme 1). In our hands, such a reaction led to the formation of the corresponding azo derivatives **4**. When the latter were treated with sodium ethoxide in ethanol, the products isolated were not the thiohydrazonates **5** (expected products of the Japp–Klingemann reaction) but the thiohydrazides **7** (products of rearrangement of **5**) (Scheme 1). Apparently, this finding represents the first case of *in situ* formation and rearrangement of thiohydrazonate esters.

The requisite active 1,2,4-triazol-5-ylthiomethylene compounds **3a**–**c** were prepared by the reaction of 3,4-diphenyl-1,2,4-triazole-5-thione **1** with the appropriate active chloromethylene compounds **2a**–**c** in ethanol in the presence of triethylamine at room temperature (Scheme 1). The structures of **3a**–**c** were established from microanalyses and from the mass, IR and ^{1}H NMR spectra which showed all the expected signals (see Experimental). The formation of **3a**–**c** from **1** and **2a**–**c**, respectively is analogous to the *S*-alkylation exhibited by 4*H*-1,2,4-triazole-3-thione derivatives.[5–7]

When **3a**–**c** were treated with benzenediazonium chloride in aqueous ethanol containing sodium acetate, they yielded the stable azo products **4a**–**c**, respectively (Scheme 1). In no case was the expected Japp–Klingemann product **5** produced. Structural assignments of the products **4a–c** isolated were made on the basis of their mass, ^{1}H NMR and IR data (see Experimental).

When **4a**–**c** were treated with sodium ethoxide in ethanol at room temperature, they afforded products that can be assigned either the thiohydrazonate structure **5** or the thiohydrazide structure **7** (Scheme 1). On the basis of their microanalyses, IR and ^{1}H NMR spectra (see Experimental), structure **5** was tentatively excluded and the products isolated were assigned the structures **7a**–**c**. However, since assignment of structures **5** or **7** is somewhat equivocal, the ^{13}C NMR and mass spectra of the products were further examined and compared with those of the model phenyl thiohydrazonate esters **9a**–**c** (Scheme 2). The latter esters **9a**–**c** were prepared by reaction of sodium thiophenolate with the hydrazonoyl chlorides **8a–c**, respectively



Scheme 1 **a**: R = PhNHCO; **b**: R = EtOCO; **c**: R = Ac

(Scheme 1). Their structures **9a**–**c** were established from their microanalyses and from their IR, ^{1}H and ^{13}C NMR spectra (see Experimental in full text version) and were confirmed by examination of their mass spectra. As with *p*-nitrophenyl *N*-arylbenzenecarbothiohydrazonates, loss of the elements of thiophenol from the molecular ions was a characteristic feature of the mass spectra of **9a**–**c**.

A comparison of the ^{13}C NMR spectra of the products, isolated from treatment of **4** with ethanolic sodium ethoxide, with those of the model thiohydrazonates **9** (Scheme 2) immediately ruled out the thiohydrazonate-type structure **5** in that no up field signal near δ 141–142 characteristic of a –S–C=N–NH– group was observed; instead the spectra revealed a thiohydrazide carbon signal near δ 155–156. Further evidence in support of structure **7** for the products isolated derives from a comparison of their mass spectra with those of **9a**–**c**. Thus, while the spectra of the products **7a**–**c** revealed in all cases the absence of peaks corresponding to the loss of 3,4-diphenyl-1,2,4-triazole-5-thiol from the molecular ions, they exhibited a characteristic peak, at *m*/*z* corresponding to ($M^+ - RCOCSN$) species, thus providing additional evidence that the products isolated are thiohydrazides **7a**–**c** and not the isomeric thiohydrazonate esters **5a**–**c**. The mass spectra of both aryl and heteroaryl thiohydrazonates were reported to be characterized by the loss of the elements of the corresponding arenethiol and heteroaryl thiol from their molecular ions, respectively.[2]

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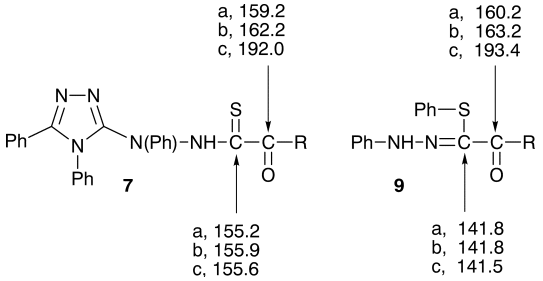

Scheme 2 **a**: R = PhNH; **b**: R = EtO; **c**: R = Me

As the Japp–Klingemann reaction is known to lead to hydrazone derivatives as the end products, it is not unreasonable to assume, on the basis of the foregoing results, that the thiohydrazonate esters **5a**–**c** undergo *in situ* rearrangement as soon as they are formed under the reaction conditions employed for the thiohydrazides **7**, probably *via* the spiro intermediates **6** (Scheme 1). In order to substantiate this suggested pathway, the reactions of **1** with hydrazonoyl chlorides **8a**–**c** were investigated. In our hands, when the latter reactions were carried out in ethanol in the presence of sodium ethoxide at room temperature, they afforded products identical in all respects (mp, mixed mp, IR spectra) with those of **7a**–**c** obtained above (Scheme 1). This result indicates that both transformations studied, namely [**4** + (EtO^-) → **7**] and [**1** + **8** (EtO^-) → **7**] proceed *via* the same intermediates **5** and **6** (Scheme 1). Regardless, however, of whether the spiro derivative **6** is involved as intermediate, the conversion **5** → **7** can be seen as an example of the Smiles rearrangement.[8,9] Several heteroaryl thiohydrazonates, prepared by treatment of the hydrazonoyl halides with (*i*) the appropriate thiol in ethanol–triethylamine or (*ii*) the sodium salt of the thiol, were reported to undergo this type of rearrangement under suitable basic conditions.[2,10,11]

Techniques used: IR, ^1H and ^{13}C NMR, MS

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