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SYNTHESIS OF α-HYDROXYAMIDES VIA THE CYANOSILYLATION OF AROMATIC KETONES[1]

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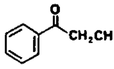
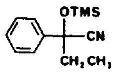
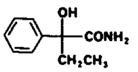
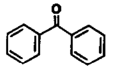
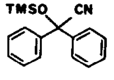
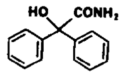
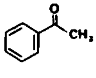
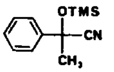
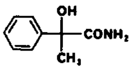
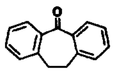
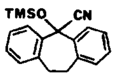
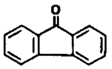
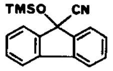
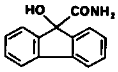
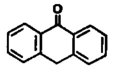
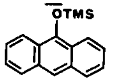
The trimethylsilyl ethers of the cyanohydrins of aryl-alkyl ketones and diaryl ketones afforded the corresponding α-hydroxyamides upon hydrolysis with HCl or HNO_3/HCO_2H. The method is advantageous for ketones that do not readily undergo addition of HCN.

Several methods are available for preparing α-hydroxyamides; some require strong base and give only the N,N-disubstituted amide.[4,5] A common method for preparing unsubstituted α-hydroxyamides involves the equilibrium addition of HCN to aldehydes and ketones to form the cyanohydrin, which is then hydrolyzed in concentrated acid to give the α-hydroxyamide.[6] While this method is efficient for most aldehydes and aliphatic ketones, the unfavorable equilibrium for the addition of HCN to conjugated aromatic ketones results in a prohibitively low conversion to the α-hydroxyamide. In some cases, such as benzophenone, the cyanohydrin will not form using this procedure. We report here a modification employing trimethylsilyl cyanide (TMSCN) which extends the usefulness of this approach to many conjugated aromatic ketones.

TABLE 1

A	A $\xrightarrow{\text{TMSCN}}$ B	B $\xrightarrow[\text{HCl}]{\text{CONC.}}$ C (ISOLATED % YIELD FROM A)	A	A $\xrightarrow{\text{TMSCN}}$ B	B $\xrightarrow[\text{HCl}]{\text{CONC.}}$ C (ISOLATED % YIELD FROM A)
 1	 2	 3 (75-90)	 10	 11	 12 (0;30[a])
 4	 5	 6 (73)	 13	 14	
 7	 8	 9 (71)	 15	 16	

[a] EMPLOYING HNO_3-HCO_2H FOR THE HYDROLYSIS

It has been reported[7,8] that TMSCN adds to aldehydes and ketones, including those to which HCN addition is unfavorable, in high yield to give the trimethylsilyl cyanohydrin ether (*e.g.* 2 in Table 1). In contrast to the addition of HCN, the addition of TMSCN is not an equilibrium process. While adducts such as 2 have been reduced to ethanolamines[8] and hydrolyzed to cyanohydrins,[9] their hydrolyses to α-hydroxyamides have not been investigated.

As part of another study we were interested in an efficient synthesis of α-ethylmandelamide (3) from propiophenone (1). We originally prepared 3 by adding HCN to 1 and hydrolyzing the equilibrium cyanohydrin mixture in concentrated HCl,[6] but this procedure provided only a 30% yield of 3. The low yield was presumed to be due to an unfavorable equilibrium for formation of the cyanohydrin. In contrast, TMSCN added to propiophenone in quantitative yield to give 2, and treatment with concentrated HCl as before gave the desired amide 3 in overall yields ranging typically from 75-90%.

This success prompted us to investigate further examples employing the above procedure. These results are summarized in Table 1. In a typical procedure, 5 mmol of the ketone was dissolved in 5 mmol of TMSCN, and 5 mg of ZnI_2 (or 0.1 mmol of KCN and 0.1 mmol of 18-Crown-6) was added as catalyst. The mixture was stirred with exclusion of moisture for 1-5 hours as determined by disappearance of the C=O stretching peak in the IR spectrum of the reaction mixture. Concentrated HCl (4 ml) was added, and HCl gas was bubbled through the stirred mixture for one hour. Neutralization and extraction with ethyl acetate provided the α-hydroxyamide product.

As illustrated in Table 1, the aryl-alkyl ketones 1 and 4 reacted to give high yields of the α-hydroxyamide. However, the results were not consistently good with diaryl ketones. While 9-fluorenone (7) gave a 71% yield of α-hydroxyamide 9, the trimethylsilyl cyanohydrin ether of benzophenone (11) did not yield any α-hydroxyamide upon treatment with HCl but gave a 30% yield of benzilamide (12) when treated with a HNO_3-HCO_2H mixture.[10] Dibenzosuberone (13) did not yield any amide. Also, a limitation of the ability of TMSCN to add to ketones was uncovered with anthrone (15) for which the reaction with TMSCN gave a high yield of the aromatic ether 16.

While the reasons for the erratic results seen for the diaryl ketones remain unclear, the above method offers significant advantages for the preparation of α-hydroxyamides from aryl-alkyl ketones and some diaryl ketones.

REFERENCES AND NOTES

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2. NIH Predoctoral Trainee (Training Grant GM 1341).
3. NSF Undergraduate Research Participant (Grant SMI-76-03091).

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