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EFFECTS OF ACID STRENGTH ON SCHMIDT REACTIONS OF ALKYL CYCLOPROPYL KETONES[1a]

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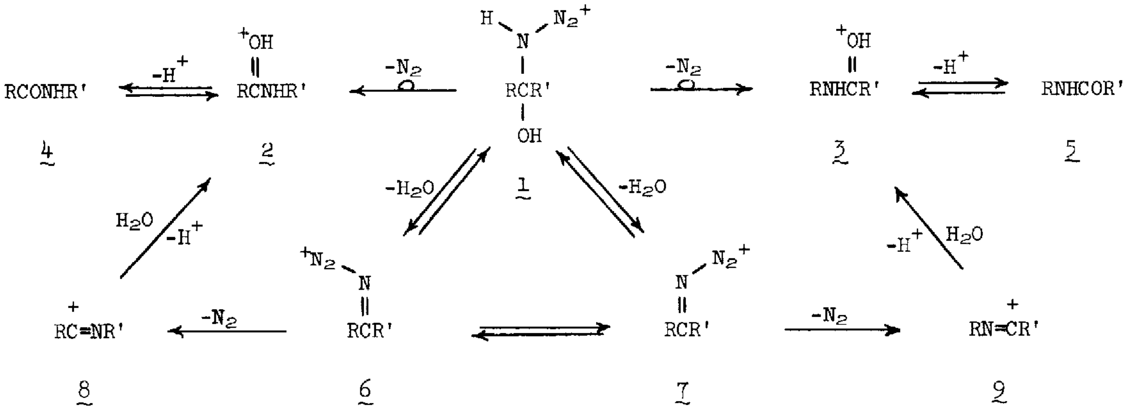
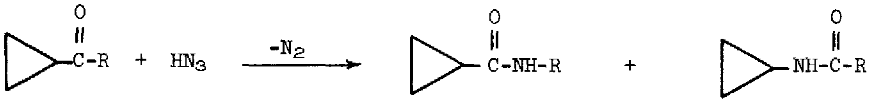
Acid-catalyzed reactions of ketones with hydrazoic acid (Eq 1) to give amides 4 and 5 (Schmidt reactions) are postulated to occur by (a) rearrangement of 1 with loss of nitrogen, or (b) dehydration of 1, *trans* rearrangement of 6 and 7 with nitrogen expulsion, and hydration of 8 and 9.[1b] In the first mechanism, the ratio of isomeric amides produced will be strongly



(1)

influenced by the abilities of R and R' to migrate.[1b] In the second mechanism, the ratio of amides will be determined primarily by the different steric repulsions in the transition states for dehydration of 1 to 6 and 7, except if isomerization of 6 and 7 is appreciably faster than their rearrangement, in which case migratory aptitudes will affect the product proportions.[1b] Schmidt reactions of most unsymmetrical ketones result in preferential migration of the bulkier substituent and are interpretable in terms of the second mechanism.[1b] A few ketones however are presumed to react via rearrangement of 1,[1c-e] and kinetic evidence indicates that the mechanisms of Schmidt reactions of alkyl phenyl ketones change as acid strength is varied.[1f] As yet there are no examples in which the ratios of amides from Schmidt reactions of unsymmetrical aliphatic ketones change with acid strength. *The present report is a study of the effects of acid strength and mechanistic differences on the reactions of alkyl cyclopropyl ketones and cyclopropyl phenyl ketone with hydrazoic acid.*

The data in Table 1 for reactions of alkyl cyclopropyl ketones with hydrazoic acid (Eq 2) reveal a dramatic dependence of the amide ratio upon acid strength. The proportions of amides



(2)

10 11 12

are essentially reversed in media of low acid strength (50% H_2SO_4 or CCl_3CO_2H) compared to high acid strength (83% H_2SO_4). Also, at all concentrations of H_2SO_4, the migration order for alkyl groups (relative to cyclopropyl) is Me > Et > i-Pr. Such an order has never been previously observed for Schmidt reactions of ketones; the usual migration order is i-Pr > Et > Me.[1a,b,c]

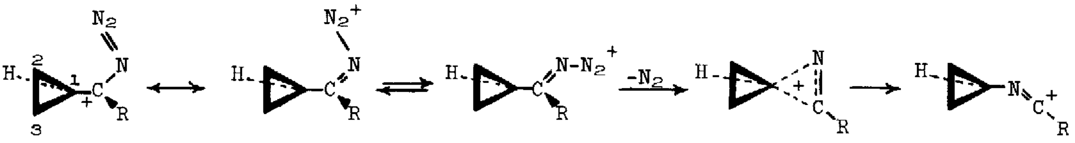
TABLE 1

Alkyl:Cyclopropyl Migration Ratios in Schmidt Reactions of Alkyl Cyclopropyl Ketones[a,b]

Acid Catalyst	R:Cyclopropyl Migration Ratio (11:12)[c] R = Me	 R = Et	 R = i-Pr
89% H_2SO_4[d]	27:73	---	---
83% H_2SO_4	26:74	18:82	8:92
69% H_2SO_4	56:44	18:82	4:96
50% H_2SO_4	90:10	74:26	18:82
CCl_3CO_2H	73:27	74:26	52:48

[a] Reactions with H_2SO_4 were run in $CHCl_3$ at 23 ± 3°; those in CCl_3CO_2H were run at 61 ± 1°. [b] Yields ranged from 88-97%. [c] By glc and nmr of the amides. [d] In 89% H_2SO_4 hydrolysis of N-cyclopropylacetamide to propanal and acetamide occurs.[1g]

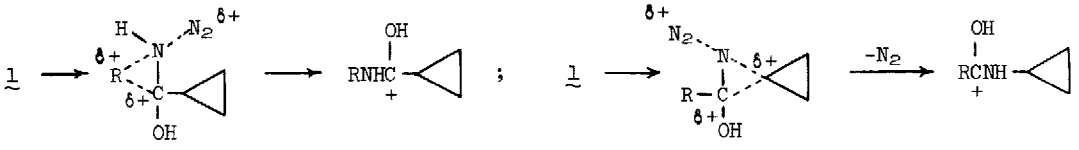
In 83% H_2SO_4 the percent cyclopropyl migration increases as the steric bulk of the group opposite it in the ketone increases, a result clearly contrary to the prediction that steric repulsions in the transition states leading to 14 and 15 are responsible for the observed amide ratios. However, in 83% H_2SO_4 the reactions may proceed via 14 and 15 which isomerize readily to one another, since the double-bond character of the imino linkages may be greatly reduced as illustrated in 13, allowing migration aptitudes to determine the amide ratios. Cyclopropyl, rather than alkyl, migration to unsaturated cationic nitrogen might occur because of ring-edge participation or perhaps more favorably by participation of the back lobes of cyclopropyl ring orbitals (C-1,2 and C-1,3) as in transition state 16.[1g,h]



13 14 15 16 17 (3)

The migration order (relative to cyclopropyl) of Me > Et > i-Pr in 83% H_2SO_4 may reflect some combination of several factors: (1) increasing stability of 16 arising from inductive electron release by R in the expected order i-Pr > Et > Me, (2) greater hyperconjugative stabilization of the transition states for migration of the less highly branched alkyl groups in 14,[1i] and (3) sterically accelerated cyclopropyl migration from 15 when R is i-Pr (and to a lesser extent, Et).

The profound increase in alkyl migration as acid strength is reduced (Table 1) suggests that in 50% H_2SO_4 and in CCl_3CO_2H reactions occur predominantly by rearrangement of 1. In transition states 18 and 20, due to the presence of the OH group, considerable positive charge may reside on the migration origin, so that 18 and 20 would resemble products 19 and 21, respectively. Thus methyl or ethyl migration, rather than cyclopropyl, may arise from stabilization of 18 (R = Me, Et) by cyclopropylcarbinyl resonance.[1j] In contrast, at high acid strengths in which dehydration to 14 and 15 is likely, there presumably is considerable positive charge at the migration terminus, which might be stabilized by cyclopropyl migration as in 16.



18 19 20 21 (4)

The proposal that at reduced acid strengths rearrangement takes place via 1 is consistent with suppositions that (1) ions analogous to 8 and 9 are not formed, since tetrazoles are not obtained at the lower acid strengths in 10 molar excess HN_3,[1k] and (2) dehydration of 1 to 6 and 7 should be less likely in the poorer dehydrating media of 50% H_2SO_4 and CCl_3CO_2H. The present data, however, for isopropyl cyclopropyl ketone suggest that dehydration of its azidohydrinium ion (**1**, R = i-Pr) is facile even in 50% H_2SO_4, possibly because of relief of steric strain. When R = i-Pr, perhaps only in CCl_3CO_2H is dehydration of **1** retarded, allowing direct rearrangement to **2** and **3**. The migration order (relative to cyclopropyl) of Me > Et > i-Pr at the lower acid strengths could result from increasing stability of **20** arising from inductive electron release by R in the expected order i-Pr > Et > Me, and/or from greater hyperconjugative stabilization of the transition states for migration of the less highly branched alkyl groups in **18**.[1i]

The phenyl to cyclopropyl migration ratio in Schmidt reactions of cyclopropyl phenyl ketone to give amides is 93 ± 2 : 7 ± 2 in all catalysts used: 69-99% H_2SO_4 and CCl_3CO_2H; reaction does not occur in 50% H_2SO_4. In these acids, Schmidt reactions of cyclopropyl phenyl ketone may proceed via analogs of **6** and **7** since dehydration to these conjugated ions should be so facile.

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