Samarium(II) Iodide Promoted Fragmentation and Sequential Reactions of Aromatic 1,4-Diketones

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Received December 9, 1999

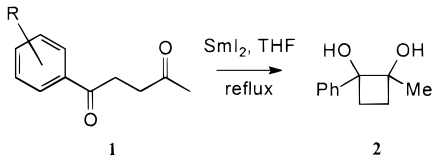
Introduction

Since its introduction by Kagan,[1] samarium(II) iodide has found manifold applications in organic chemistry. This powerful one-electron reductant has been extensively employed in standard reduction reactions,[2] where it shows remarkable selectivity. Carbon−carbon bond-forming reactions have been explored in some detail,[2−4] as have carbon−heteroatom bond fragmentation reactions.[2] The facility with which SmI_2 may be incorporated into reaction sequences involving highly functionalized compounds is attested by the many publications describing the employment of this reducing agent in key steps.[5]

Although much of the research making use of SmI_2 has focused primarily on bond-forming reactions, a number of fragmentation reactions have been reported. The majority of said fragmentation reactions have, thus far, been aimed at carbon−heteroatom bond cleavage.[2] A few accounts of carbon−carbon bond cleavage have been forthcoming,[6] but these have been sparse. In most of these disclosures, ring-strained systems have been the subjects of the fragmentation reactions.[6a−e] In one case,[6f] a substrate that possessed little ring strain (a γ-haloester cyclopentane derivative) was employed, while in another a 3-oxo-1,4-diene steroid was observed to undergo ring scission.[6g] Simple reductive dehalogenation was found to compete with bond cleavage in the former case. As part of our continued investigations into reactions promoted by SmI_2, including fragmentation processes,[7] we became interested in cleavage reactions of 1-aryl-1,4-diketones. We herein wish to report on the carbon−carbon bond cleavage of a variety of *open chain* 1-aryl-1,4-diketones.

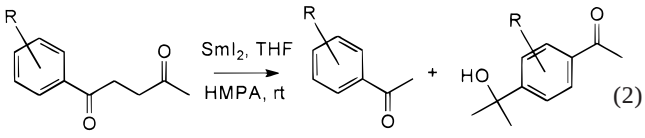
Results and Discussion

Initial probes made use exclusively of 4-oxo-valerophenone (**1**, R = H).[8] Hoffmann has described the cyclization reaction of 1,4-diketones to produce 1,2-cyclobutanediol derivatives (including that derived from **1**, R = H, in a yield of 88%),[9] while Ghosh has described the fragmentation of some strained systems when incorporating HMPA into the reaction mixture.[6e] When following the exact experimental description of Hoffmann (SmI_2 in THF under reflux),[9] we were easily able to repeat those results (affording the corresponding substituted 1,2-cyclobutanediol) with no observable side reactions (eq 1). An analogous reaction was carried out using the *p*-chloro-substituted equivalent of **1** (R = Cl), with similar results.



1 **2** (1)

In stark contrast, repetition of the above reaction at room temperature in the presence of HMPA (similar to the conditions specified by Ghosh[6e]) afforded a more complex mixture of products, consisting primarily of acetophenone and the product of phenyl-carbonyl coupling[10] (eq 2; entry 1 of Table 1). The isolation of these products indicated that the presence of HMPA facilitated carbon−carbon bond cleavage. The mechanisms of elimination (fragmentation) reactions from intermediate ketyl-radicals have previously been described as proceeding via radicals[6a] or anions,[11] depending on the substrate. The exact mechanism of the current fragmentation reaction is currently unknown.



1 **3** **4** (2)

A plausible explanation for the selectivity for fragmentation over pinacol cyclization observed in the presence of HMPA might be found in competitive complexation. It is expected that, in the presence of HMPA, only one of the carbonyl moieties can coordinate the SmI_2-$HMPA_n$ complex,[12] while in the absence of HMPA both carbonyl moieties can coordinate the SmI_2-THF_n complex,[3,13] thus leading to pinacol cyclization in the latter case and fragmentation in the former.

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10.1021/jo9919005 CCC: $19.00
Published on Web 04/07/2000

Table 1. Results of Fragmentation Reactions of 1 (R = H) under Various Conditions[a]

entry	H^+ source (5 equiv)	temp (°C)	addition[b] (SmI_2 equiv)	recovery of **1** (%)	yield of **3** (%)	other products (%)
1		25	normal (4.8)	0	28	**4** (21) **7** (6)
2		−78	normal (2.4)	25	7	
3	MeOH	25	normal (3.8)	8	10	**4** (34)
4	MeOH	−78	normal (2.2)	70	7	
5	MeOH	25	reverse (2.2)	17	20	
6	PhOH	25	reverse (2.2)	41	33	
7	PhOH	25	reverse (3.3)	12	47	**5** (10) **6** (18)
8	PhOH	25	normal (4.8)	33	22	**4** (10) **6** (10)
9	PhOH	25	normal (7.2)	0	9	**4** (17) **6** (15)
10	EtOH (253 equiv)	25	reverse (3.3)	33	5	**5** (5)
11	EtOH	25	reverse (4.8)	15	3	**4** (10)

[a] Yields refer to those of isolated products. [b] Addition: "normal" implies the addition of substrate in THF to a solution of SmI_2 in THF/proton source; "reverse" implies SmI_2 solution in THF added to the solution of diketone in THF/proton source. In all cases, 8 equiv of HMPA were added to the SmI_2/THF solution.

Upon further investigation, it became clear that the type and yield of products (Figure 1) isolated[14] from the above reaction were somewhat sensitive to reaction conditions.

The findings of the preliminary investigations are summarized in Table 1. The results show changes that occurred in product distribution with changing reaction conditions (temperature, proton source, equivalents of added SmI_2). It is of interest to note that, contrary to the expected preferential reduction of the aromatic ketone,[15] the aliphatic alcohol **6** was obtained (as opposed to the benzylic alcohol) as one of the products when phenol was employed as a proton source (entries 7−9). The exact reasons for this reversal of selectivity are unclear, but it may be the result of protonation (and hence activation) of the more basic aliphatic carbonyl by this relatively acidic alcohol.[16] It was also of some surprise to note that products of phenyl-carbonyl coupling were isolated when the reaction was carried out in the presence of a proton source, even when that source was relatively acidic

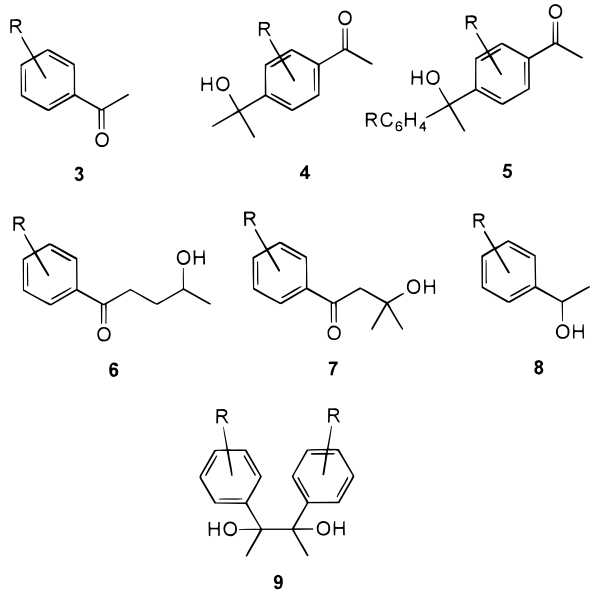

Figure 1. Products obtained by reaction of **1** with SmI_2/THF/HMPA.

(entries 6−9) or was present in an overwhelming excess (entry 10). This observation lends credence to the radical pathway proposed as a mechanism by Fang,[10] as opposed to the alternative ionic mechanism, for the phenyl−carbonyl coupling reaction. It is clear from the table that low temperatures (entries 2 and 4) inhibit the desired fragmentation reaction. It is also apparent that, while substantial yields of products of sequential reactions were obtained (thereby complicating the product mixtures), the total fragmentation yield was satisfactory in most cases (up to 75%, entry 7).

The fragmentation methodology was subsequently applied to various other functionalized aromatic diketones. The results, summarized in Table 2, evidence the fact that *para* or *ortho* substitution on the arene drastically reduces the complexity of product mixtures and largely prevents the sequential reactions previously observed (even though the *para* position was open in the *ortho* substituted substrates, only small amounts of the corresponding product **4** were obtained). Once again, total product derived from fragmentation is high in certain cases (up to 75%, entry 7). Although not shown in Table

(14) The identities of starting materials and products were confirmed primarily by comparison with previously published data. The literature references for the individual products are as follows: starting materials **1**, refs 8 and 9 and refs therein; **2**, ref 8; **3** (R = H), data compared with those of an authentic sample; **3** (R = *p*-Cl), *The Aldrich Library of NMR Spectra*; The Aldrich Chemical Co. 1974; Vol. VI, p 21, spectrum A.; **3** (R = *o*-Cl), Kikukawa, K.; Idemoto, T.; Katayama, A.; Kono, K.; Wada, F.; Matsuda, T. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1511; **3** (R = *p*-OMe), *The Aldrich Library of NMR Spectra*; The Aldrich Chemical Co., 1974; Vol. VI, p 27, spectrum B.; **4** (R = H), Olah, G. A.; Berrier, A. L.; Prakash, G. K. S. *J. Org. Chem*. **1982**, *47*, 3903; **5** (R = H), Martre, A. M.; Mousset, G.; Pouillen, P.; Prime, R. *Electrochim. Acta* **1991**, *36*, 1911; **6** (R = H), Chini, M.; Crotti, P.; Favero, L.; Pineschi, M. *Tetrahedron Lett*. **1991**, *32*, 7853; **7** (R = H), Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc*. **1974**, *96*, 7503; **8** (R = *p*-OMe), *The Aldrich Library of NMR Spectra*; The Aldrich Chemical Co., 1974; Vol. V, p 11, spectrum B.; **9** (R = *p*-OMe), Leimner, J.; Weyerstahl, P. *Chem. Ber*. **1982**, *115*, 3697. As far as can be established, compound **4** (R = *o*-Cl) has not been previously prepared (CAS online search). As a result of the very low yield of this material, extensive analytical data are not available. The identity of this product was established by comparison of available data with those of its analogue (**4**, R = H) and of the starting diketone. R_f 0.2 (hexanes/EtOAc = 3:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (d, 1H, J = 1.6 Hz), 7.54 (d, 1H, J = 8.2 Hz), 7.40 (dd, 1H, J = 8.2 and 1.6 Hz), 2.64 (s, 3H), 1.56 (s, 6H); MS (EI) *m*/*z* (rel intensity) 212 (M^+, 10%), 197 (100), 154 (50).

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(16) One referee suggested that product **6** might have resulted from an intramolecular Meerwein−Ponndorf−Verley/Oppenauer reaction after the reduction of the ketone adjacent to the phenyl group by SmI_2 as is normally anticipated. We thank the referee for this comment.

Table 2. Reaction of Substituted Diones with SmI_2

entry[a]	substrate R =	addition[b]	yield of **3** (%)	other products (%)
1	*p*-Cl	normal	32	
2	*p*-Cl	normal[c]	56	
3	*p*-Cl	reverse	17	**1** (5)
4	*o*-Cl	normal	15	**4** (4)
5	*o*-Cl	reverse	10	
6	*p*-OMe	normal	31	**8** (12)
7	*p*-OMe	reverse	43	**8** (19)
				9 (13)
8	H	normal	34	**4** (16)
				5 (19)
9	*p*-Cl	normal	85	
10	*o*-Cl	normal	26	**4** (14)
11	*p*-OMe	normal	35	**8** (23)
				9 (23)

[a] Reactions corresponding to entries 1−7 were carried out at ambient temperature, and those corresponding to entries 8−11 were carried out at the reflux temperature of the mixture. [b] Addition: "normal" implies the addition of substrate in THF to a solution of SmI_2 in THF/proton source (7 equiv); "reverse" implies SmI_2 solution in THF added to the diketone solution in THF/proton source (7 equiv). In all cases, 8 equiv of HMPA were added to the SmI_2/THF solution, and 3.3 equiv of SmI_2 were routinely used. [c] Reaction conditions similar to those given in footnote *b*, but 4.8 equiv of SmI_2 were employed.

2, the furyl analogue of dione **1** was also subjected to these reaction conditions. Apart from a small amount (7%) of the "*para*" substituted equivalent of **4**, no other products of fragmentation were observed. Entries 8−11 detail the findings of similar reactions carried out at the reflux temperature of the reaction mixture. The most striking feature of the latter set of reactions is the improvement of the overall fragmentation yield (up to 85%, entry 9) in three of the four cases (all of which were the more highly substituted systems). The primary reason for the improved yield seems to be the result of a diminished competition between the fragmentation reaction and side-reactions (over-reduction, phenyl−carbonyl coupling, pinacol coupling, etc.). The reason for this observation may lie in the fact that fragmentation reactions in which there is a gain in entropy (two molecules from one) are in general favored by an increase in the reaction temperature.[17]

Conclusion

The results presented in this note clearly indicate that the presence or absence of HMPA in the reaction mixture is the deciding factor that determines the outcome (reductive fragmentation or cyclization) of the reaction of 1-aryl-1,4-diketones with SmI_2. This represents another example of the dramatic effect that HMPA can have on the outcome of a Sm(II)-mediated reaction. It has also been shown that the specific reaction conditions greatly influence the outcome of said fragmentation and/or subsequent reactions, as does the substitution pattern on the arene.

Experimental Section

All reactions were carried out in flame-dried glassware under a positive pressure of argon. Solvents and cosolvents were distilled from the appropriate drying agents (THF from sodium−benzophenone ketyl, HMPA from CaH_2, and lower alcohols from magnesium alkoxide) and were degassed by purging with argon or using a freeze−pump−thaw routine. Starting materials were obtained from the Stetter reaction of the corresponding aldehydes.[8] All solid materials were thoroughly degassed directly prior to reaction with SmI_2 by repetitive evacuation of the gases and filling of the reaction vessel with argon. SmI_2 (0.1 M) was prepared by the reaction of a suspension of Sm metal in THF with freshly recrystallized diiodoethane.

Reaction conditions for preparing four-membered rings via the pinacol coupling reaction have been detailed[9] and were employed here exactly as described. Reaction conditions used for fragmentation reactions have been disclosed[6e] and were used here as described.

JO9919005

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