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"SELECTIVE REDUCTION OF ISOXAZOLES WITH SAMARIUM DIIODIDE"

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Summary Samarium diiodide is an efficient reagent for the reductive cleavage of the O-N bond of isoxazoles Olefins, esters, and acetals are stable to the reaction conditions, benzylic halides and aldehydes are not

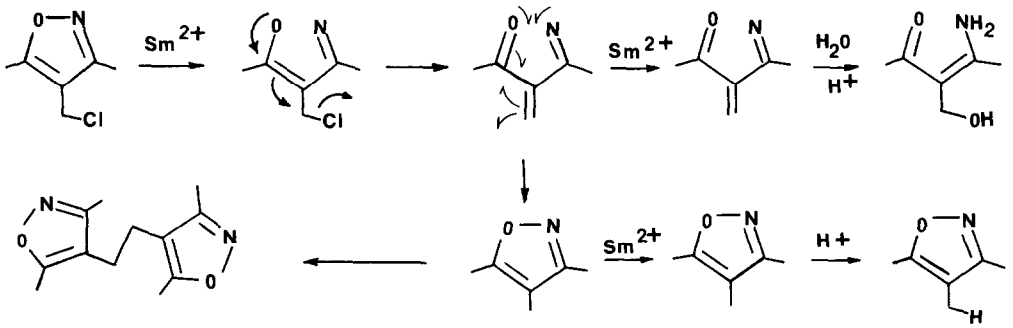
The utility of the lanthanide elements in synthesis has only recently been appreciated by organic chemists This is in large part due to the pioneering efforts of the groups of Kagan[1] and Luche [2] Luche and colleagues have discovered several practical lanthanide(III) mediated synthetic methods including the selective 1,2-reduction of conjugated enones,[2a] and the reduction of ketones in the presence of aldehydes [2b] Kagan and coworkers have explored the reducing properties of lanthanide(II) reagents Thus ketones and aldehydes are reduced to alcohols, halides are effectively reduced to hydrocarbons, epoxides and sulfoxides deoxygenated, and an effective lanthanide Barbier reaction has been explored [1a] A recent report by Magnus on the use of samarium diiodide for the deprotection of chloro carbonates and xanthates further illustrates the potential of this electron transfer reagent [3] With this communication, we wish to report the reductive cleavage of isoxazoles with samarium diiodide

Treatment of 3,5-dimethyl isoxazole with two equivalents of a deep-blue solution of samarium diiodide in THF at room temperature for one hour, with methanol as a proton source, cleanly affords the enamino ketone (Table, Entry 1) The upfield chemical shift of the signals in the NMR of the purified product, as well as the IR absorbances are consistent with the destruction of the aromatic ring [4] Similarly the isoxazole ester[5a] (Entry 2) gives clean cleavage to the enamino ketone The resulting enamino ketones are somewhat unstable, but can be stored after purification, under inert atmosphere at 0° C

In the course of an investigation which utilized an isoxazole as a 1,3-dicarbonyl synthon, we wished to perform an efficient halogen lanthanide exchange on the 4-chloromethyl-3,5-dimethylisoxazole[5b] (Entry 3). We found that the ring opened alcohol [6] was produced in 80% yield accompanied by the desired metalated species (13%)[7] and a small amount of isoxazole dimer(2%)[8]. Since the starting material is stable under the work-up

conditions, the major product is obtained via hydrolysis after ring opening If this same reaction is allowed to proceed for two days at room temperature, in the absence of a proton donor, the isoxazole dimer becomes the major product (54-60%) A mechanism which accounts for the observed products is shown in Scheme I This takes into account the observation of Kagan[1b] that the reaction of SmI_2 with ketones is free radical in nature, and involves no metal-carbon bond formation

In the case of the isoxazole bromide (Entry 4), in sharp contrast, the major resultant products arise from (in effect) efficient halogen-lanthanide exchange 3,4,5-trimethyl isoxazole (36%) and dimeric product (47%)



Finally, we have explored the use of the lanthanide isoxazole cleavage in a spiro annulation sequence Reaction of SmI_2 with the aldehyde isoxazole[9] (Entry 5), however, gave exclusively the alcohol isoxazole[10] (53% after ptlc) Acetals[11] are stable to the reaction conditions, and conversion to the cyclohexenone[12] (entry 6) is accomplished in 78% yield overall from the aldehyde isoxazole.

In summary, samarium diiodide is an efficient reagent for the reductive cleavage of the O-N bond This reagent system has the following advantages the reaction may be conducted in aprotic media and does not have the complication of competitive reduction of olefins We are currently investigating the application of this intriguing reagent system to other problems in heterocyclic chemistry

General Experimental A ca. 10^{-2} M solution of SmI_2 in THF was prepared according to the procedure of Kagan[1a] The deep-blue solution (ca 2 eq SmI_2)[1b] was transferred via syringe to a solution of isoxazole (1 mmole) in THF (2 mL). After the prescribed time, methanol was added (1 mL), the THF concentrated, cold aqueous NH_4Cl added (25 mL) and the mixture extracted with methylene chloride (3 x 25 mL) The combined organic extracts were dried (K_2CO_3) filtered and concentrated Purification was effected by preparative gc or thin layer chromatography

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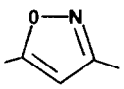
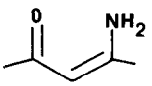
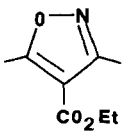
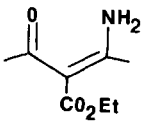
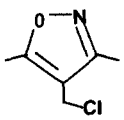
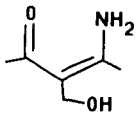
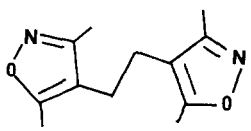
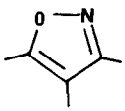
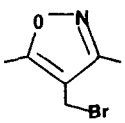
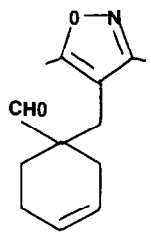
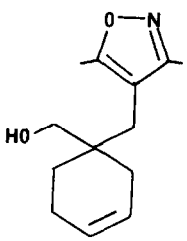
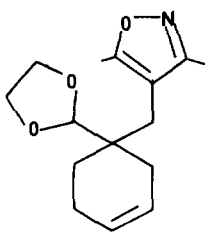
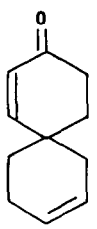
TABLE Reductive cleavage of Isoxazoles with samarium diiodide.

Entry	Isoxazole	Time	Product(s)	Yield[a]
1		1 h		57
2		1 h		96
3				
		1 h 80	2	13
		2 d ...	54-60	...
4		3 h <1	47	36
5		24 h		53
6		24 h[b]		78

[a] Products were isolated by preparative gc or ptlc [b] converted to enone[12a] directly

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4 (a) Purified by preparative gc (SE-52, 150° C)
nmr ($CDCl_3$) - δ5.1, s, IH, 2 1, s, 3H, 2.0, s, 3H Ir - 3340, 3180, 1620, 1530
gc/ms -m/z 99 (58% R I), 84 (100), 43 (22), 42 (56)
(b) Claisen, L , Ber Deut Chem. Ges , 1891, 24, 3900
(c) Buchi, G , and Vederes, J C , J Am Chem Soc , 1971, 92, 9128

5 (a) Stork, G , and McMurry, J , J Am Chem Soc , 1967, 89, 5463. (b) Kochetkov, N K , Khomutova, E D , Kapeysky, M J , and Khomutov, R M , Zhur Obschei Khim , 1957, 27, 3210

6 Purified by preparative gc (3% OV-1, 6', 100° initial, 15°/min).
nmr - δ3 68, s, 2H, 2 23, s, 3H, 2 16, s, 3H Ir - 3400, 1155, 685 gc/ms - m/z 127 (15), 110 (100), 68 (62)

7 Purified by preparative gc (3% OV-1, 6', 100° initial, 15°/min)
nmr - δ2.27, s, 3H, 2 16, s, 3H, 1 85, s, 3H gc/ms - m/z 111 (100% R I), 96 (64), 82 (12), 68 (83)

8 Purified by preparative gc (3% OV-1, 6', 100° initial, 15°/min) ptlc (Al_2O_3, CH_2Cl_2) Rf 0 52, or column chromatography (Florosil, $CHCl_3$)
nmr - δ2 6, s, 4H, 2 32, s, 6H 2 28, s, 6H Ir - 1640, 1455, 1435, 1200, 890
gc/ms - m/z 220 (47% R I), 205 (87), 110 (100)

9 Prepared from 1,2,5,6-tetrahydro benzaldehyde via its (RS)-1-phenyl-2-amino-3-methoxy-propane imine, by deprotonation (LDA, 0°) alkylation with 4-chloromethyl-3,5-dimethyl isoxazole (-78°) and hydrolysis (1 N aq HCl/CH_2Cl_2) ptlc (SiO_2, CH_2Cl_2, R_f 0 3)
nmr - δ9 5, s, 1H, 5 7, s, 2H, 2 5, s, 2H, 2 3, s, 3H, 2 2, s, 3H
Ir - 1720, 1630 ms-m/z 219 (5 1% R I), 110(100) RP HPLC (μCH-10, 30% MeOH/H_2O flow rate 1 mc/min) Rf 6 2 min The possibility that chiral imines in the above sequence will provide an asymmetric annulation is under active investigation

10 ptlc (Al_2O_3, CH_2Cl_2, R_f 0 7) b p 150° (4 mmHg) Kugelrohr
nmr - δ5 5, 2H, 3 29, 2H, 2 25, s, 3H, 2 13, s, 3H Ir - 3400, 1620, 1440, 1420, 1195, 1040 gc/ms - m/z 221 (6% R I), 203 (10), 160 (22), 112 (28), 93 (46), 43 (100)

11 Prepared from aldehyde isoxazole (ref 9) (ethylene glycol, TsOH, Ph, reflux)
nmr - δ5 62, br s , 2H, 4 73, S, 1H, 3 9, m, 4H, 2 43, s, 2H, 2 33, s, 3H

12 (a) Scott, J W , Bannor, B L , Saucy, G , J Org Chem , 1972, 37, 1664-1665
Product was identical to material prepared according to (b) Flaugh, M. E , Crowell, T A , Farlow, D S , J Org Chem 1980, 45, 5399-5400

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