Tetrahedron Letters, Vol. 34, No. 12, pp. 1871-1874, 1993 Printed in Great Britain

New Alkane Functionalization Reactions Based on Gif-Type Chemistry in the Presence of Alkali Metal Salts.

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<u>Abstract</u>: Cycloalkanes are transformed into monosubstituted cycloalkyl derivatives (chloride, azide, cyanide, thiocyanate, dicycloalkyl disulfide, or nitroalkane) in mostly good efficiencies by treatment with *tert*-butyl hydroperoxide in pyridine/acetic acid containing Fe(NO₃)₃.9H₂O, in the presence of alkali metal salts (LiCl, NaN₃, [Et₄N]CN, NaSCN, Na₂S, or NaNO₂, respectively). In comparison, ionic trapping with Cu(OAc)₂ gave efficient trapping with chloride ion, very inefficient capture of thiocyanate, and a significant difference in reactivity towards azide ion.

Most of our efforts to activate and functionalize saturated hydrocarbons have involved $1 \text{ FeII} + \text{superoxide or FeIII} + \text{H}_2\text{O}_2$. More recently,² we have turned our attention to Fe^{III} + *t*-butyl hydroperoxide (TBHP). Although chloride and bromide ions do not participate in the earlier oxidation systems¹, we do find efficient trapping³ with a variety of anions using TBHP. The results of these experiments are shown in Table 1.⁴

All the Gif systems, including that based on TBHP (GoAgg^{IV}), involve the activation of the hydrocarbon¹ to give intermediate A (Scheme 1). This is not a carbon radical. We postulate an ironcarbon sigma bond. By insertion of oxygen and hydrolysis, intermediate B is obtained. This is the corresponding hydroperoxide, which fragments to ketone or is reduced to alcohol. In GoAgg^{IV}, intermediate A is trapped by ionic reagents. We report selected results for cyclohexane, but we have seen the same chemoselectivity with cyclopentane, cyclooctane and adamantane. Running the reactions in a partial vacuum or under argon reduced the formation of ketone and alcohol. For example, the chlorination of cyclooctane was achieved in 90% efficiency running the reaction under Ar.⁵ Also, cyclooctane could be converted into its azide in 78% efficiency.⁶ Remarkably, the addition of α -picolinic acid restores the natural ketonization reaction at the expense of the chlorination process.

The appropriate blank experiments were carried out. Cyclooctanol in pyridine/acetic acid in the presence of FeCl₃.6H₂O did not afford any cyclooctyl chloride in the absence of the oxidizing reagent (TBHP). Without addition of FeCl₃.6H₂O, no chlorination of the hydrocarbons was observed. When TBHP was replace by tert-butyl hypochlorite (which could have formed in situ from TBHP and be the chlorinating reagent), the chlorination yield was only 10% of the yield from the Gif-type reaction.

Table 1. Fe (III) or Cu	¹¹ -catalyzed functionaliza	ition of saturated hydroca	irbons by TBHP in the p	resence of an alkali meta	l salt.a
Alkali Salt	Ŷ	HO	×	Total	Reaction
NaX _n (or LiX)	\supset	\supset	\supset	Products	Efficiencyf
lomm		(mmol)	i	(mmol)	(%)
FeIII					
None	5.31	0.49		5.80	58.0
LiCI (15.0)	0.72	0.17	4.98	5.87	58.7
LiCl (15.0)+					
α-picolinic acid (1.0)	1.14	0.19	5.03	6.36	63.6
LiCI (15.) +					
a-picolinic acid (3.0)	3.37	0.44	0.41	4.23	42.3
LiBr (15.0)	0.58	0.58	5.8	6.96	69.69
NaN3 (15.0)	1.54	0.11	3.66	5.31	53.1
$[Et_4N]CN (10.0) p$	0.10	0.03	0.95	1.08	10.8
NaSCN (10.0) C	0.61	0.22	2.64	3.47	34.7
NaNO ₂ (15.0) d	1.55	0.12	0.25	1.92	19.2
Na2S (8.0) e	0.16	I	0.33	0.49	9.8
CuII8					
LiCI	3.98	1.68	0.18	5.84	58.4
NaN _{3.}	0.97	2.65	0.22	3.84	38.4
NaN ₃ ^b	4.98	0.18		5.16	51.6
NaSCN	0.15	0.19	0.06	0.40	4.0
a. Reaction conditions:	TBHP (10.0 mmol), cy	clohexane (50 mmol), py	idine, (30.0 mL), acetic	acid (3.0 mL), Fe(NO ₃)) ₃ .9H ₂ O (1.0 mmol),
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disulfide. ⁹ f. For effici	eaction conditions. a.	LIE OILLY LEAUUNI PLOUUN Gerence 10. g. For exper	ci was inuccyclonexane rimental conditions see	reference 11. For effic	uct was ancycionexyl iency calculation see
reterence IU.					

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The mechanism of most of the reactions reported in this article will be discussed elsewhere. In two cases, the products define the mechanism. The bromination of cyclohexyl bromide gives mainly *trans*-1,2-dibromocyclohexane. This shows that the reaction is radical bromination (Skell-Walling effect).⁷ On the other hand, azidation of cyclohexene gave very little oxidation and 4.84 mmol of the allylic azide (from 5 mmol TBHP). In contrast,¹² anodically generated azide radicals add to cyclohexene to give the 1,2-diazide (55%) with little allylic azide (15%). So the azidation process is not a radical reaction. For the Cu^{II} reactions, chlorination is efficient, azidation is much more effected by oxygen than for the Fe^{III} reactions, but an efficient reaction under argon. In contrast to Fe^{III}, Cu^{II} gives very inefficient thiocyanation. Again, we are not dealing with a radical common to both systems.

Paraffins have historically been regarded as an inert class of organic compounds. These and previous results¹ prove that belief to be a myth. Indeed, when confronted by the appropriate chemical species, paraffins display a rich variety of functionalization reactions. This "reactive species" possesses subtly different chemical properties depending on what the starting oxidant used was (*i.e.*, hydrogen peroxide or TBHP). This explains the differences in kinetic isotope effect and chemical reactivity between the two systems.²a,g & 8

Acknowledgments. We are indebted to the National Science Foundation, British Petroleum of America and Quest International for financial support of this work.

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- Reaction conditions: cyclooctane (50.0 mmol), pyridine (30.0 mL), acetic acid (3.0 mL), FeCl_{3.6}H₂O (5.0 mmol), TBHP (10.0 mmol), under Ar, 60°C, 18 h. The reaction products were cyclooctyl chloride (8.96 mmol), cyclooctanone (0.02 mmol) and cyclooctanol (traces).
- Reaction conditions: cyclooctane (50.0 mmol), pyridine (30.0 mL), acetic acid (3.0 mL) Fe(NO₃)₃.9H₂O (5.0 mmol), TBHP (10.0 mmol), NaN₃(15.0 mmol), under Ar, 60°C, 18 h. The reaction product was cyclooctyl azide (7.79 mmol), accompanied with traces of cyclooactanone and cyclooctanol.
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- 10. The reaction efficiency is calculated considering that one equivalent of TBHP is required for the formation of the alkyl hydroperoxide, and thus keton and alcohol, as well as, for the formation of olefin, chloride, azide or thiocyanate. Two oxygen atoms from dioxygen are introduced during hydroperoxide formation, but are not included in the calculation.
- 11. Experimental conditions: Cu (OAc)₂.H₂0 (0.5 mmol), metal salt (15.0 mmol), TBHP (10.0 mmol), pyridine (30.0 mL), acetic acid (3.0 mL), cyclooctane (50 mmol), 60°, 24 h. in a closed system.
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(Received in USA 1 December 1992; accepted 12 January 1993)