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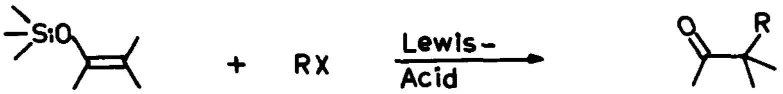
LEWIS ACID MEDIATED α-ALKYLATION OF KETONES USING S_N1 REACTIVE ALKYLATING AGENTS

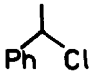
M.T.Reetz*, S.Hüttenhain, P.Walz and U.Löwe
Institut für Organische Chemie und Biochemie der Universität
Gerhard-Domagk-Str. 1, 53 Bonn, W.Germany

Summary : Alkylation of ketones via silyl enol ethers is possible using aryl activated secondary alkyl halides or thio ketals. In case of prenyl halides the ratio of primary to tertiary alkylation is governed by steric factors and by the nature of the Lewis acid.

Some recent papers by Paterson and Fleming$^{1)}$ concerning Lewis acid induced regiospecific α-alkylation of carbonyl compounds via silyl enol ethers prompt us to disclose our own results in this area. We have made similar observations, but shall concentrate here on results which go beyond or differ from those already published$^{1)}$. As indicated in our first paper describing the α-alkylation of carbonyl compounds, not only tertiary halides, but also those of the "type allyl and benzyl can be used in the same way"$^{2)}$.



Utilizing 1 - 4, the proper enol ethers and catalytic amounts of $ZnCl_2$$^{3)}$ or equivalent amounts of $TiCl_4$, we have prepared 5 - 12. Yields are based on isolated products. This shows that secondary benzylation is not restricted to halides of the type 1$^{1)}$. The advantage over classical enolate chemistry is seen in the absence of poly-alkylation, regiospecificity$^{1)}$, the formation of little or no elimination products and the ease of performance.



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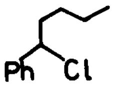

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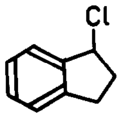

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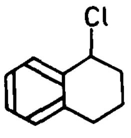

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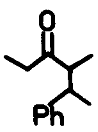

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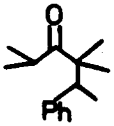

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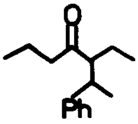

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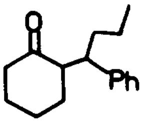

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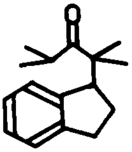

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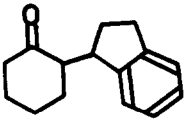

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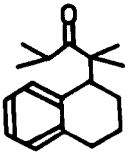

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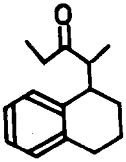
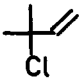


12 (65%)

We have also studied alkylations using the potentially ambident halides 13, 14 and 15. Whereas Paterson[1)] reports only primary alkylation (prenylation, i.e. attack at the less substituted C-atom) employing 15, we find that 13, 14 or 15 lead to primary *and* to tertiary alkylation, the ratio of which being dependent upon the *structure of the ketone and upon the nature of the Lewis acid*.



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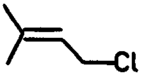

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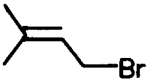

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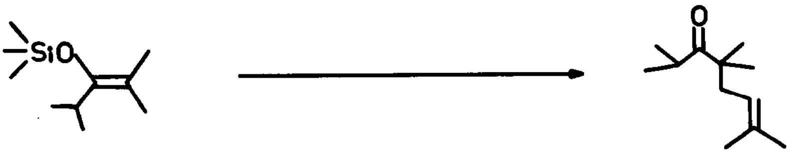
We propose the following generalizations: a) Lewis acid induced isomerization 13→14 competes with alkylation. b) If the α-position of the starting ketone bears but a single H-atom, steric factors result in clean primary alkylation (prenylation) irrespective of the nature of the Lewis acid. c) If the α-position bears at least two H-atoms, mixtures of primary and tertiary products result d) Concerning point c), ZnX$_2$ result in appreciable amounts of tertiary products (20-50%), the remaining major portion undergoing prenylation. In contrast, the *use of CuI significantly reduces the extent of tertiary alkylation*, prenylation occurring to >75%. e) Prenylations involving CuI are slower than those with ZnX$_2$, but are to be preferred in relevant cases (point d). f) Bromides react much faster than chlorides. g) Poly-alkylation is not observed.

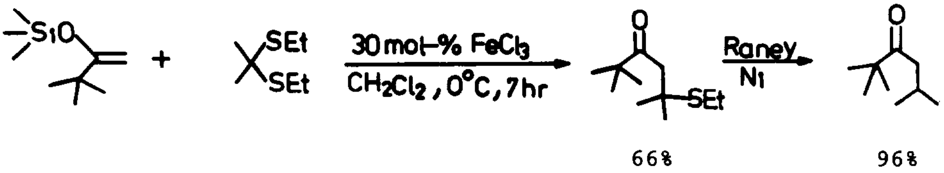
The following examples are typical:



13 /CH_3NO_2/$ZnCl_2$/22°C/1 h	95% crude	}	>75% after column chromatography
13 /CH_2Cl_2/CuI/22°C/20 d	90% crude		
14 /CH_3NO_2/$ZnCl_2$/22°C/2 h	95% crude		

13 /CH_3NO_2/$ZnCl_2$/0°C/5 min	60%	:	40%	crude 100% isolated 94%
14 /CH_3NO_2/$ZnCl_2$/0°C/15 min	60%	:	40%	crude 95%
14 /CH_2Cl_2/CuI/22°C/5 d	88%	:	12%	crude 85%
14 /no solvent/$ZnCl_2$/0°C/45 min	80%	:	20%	crude >85%
15 /CH_2Cl_2/$ZnBr_2$/0°C/5 min	50%	:	50%	crude ∿65%
15 /CH_2Cl_2/CuI/22°C/3 h	77%	:	23%	crude >80%

Non activated secondary alkyl halides such as isopropyl chloride do not undergo similar alkylations. Whereas classical enolate chemistry is often satisfactory, many cases are known in which elimination predominates. Zook has established a correlation between %-elimination and pK value of the ketone4). For example, the reaction of isopropyl halides and related secondary alkylating agents with the enolate anion of pinacolone leads to elimination and not to the desired alkylation In order to solve this type of problem, we have employed thio ketals and $FeCl_3$ as the Lewis acid catalyst, e.g.:



The above sequence (which we have found to be general) is related to Mukaiyamas version of the Aldol condensation⁵⁾. The sulfur analog described in the present paper allows for synthetic flexibility, reductive removal of sulfur as well as oxidative elimination being possible. It should be noted that Paterson and Fleming have elegantly employed primary α-halo sulfides in a related manner, a process which results in primary alkylation¹⁾. Due to the ready availability of thio ketals and acetals, we believe that our method represents a useful contribution.

Finally, we note that any S_N1 reactive molecule may be employed in Lewis acid promoted alkylations. As a further example, we find that cholesteryl chloride alkylates the silyl enol ethers of ketones.

Regarding the general procedure for secondary benzylation⁶⁾, it is very similar to our method of α-tert-alkylation of ketones²⁾. One works at -30°C to -40°C in methylene chloride as solvent and uses equivalent amounts of silyl enol ether, secondary benzyl halide and $TiCl_4$. The crude products are distilled or chromatographed over silica gel⁷⁾.

Acknowledgement: This work was supported by the Fonds der Chemischen Industrie and the Deutsche Forschungsgemeinschaft.

References and Notes:

1) I.Paterson, Tetrahedron Lett. 1979, 1519; I.Paterson and I.Fleming, Tetrahedron Lett. 1979, 995; I.Paterson and I.Fleming, Tetrahedron Lett. 1979, 2179.
2) M.T.Reetz and W.F.Maier, Angew.Chem. 90, 50 (1978); Angew.Chem.,Int.Ed.Engl. 17, 48 (1978), in particular footnote nr. 6, therein; see also T.H.Chan, I. Paterson and J.Pinsonnault, Tetrahedron Lett. 1977, 4183; concerning the use of $ZnCl_2$ as a particularly mild Lewis acid, see: M.T.Reetz and K.Schwellnus, Tetrahedron Lett. 1978, 1455.
3) $ZnBr_2$ is also suitable.
4) H.D.Zook, W.L.Kelly and I.Y.Posey, J.Org.Chem. 33, 3477 (1968).
5) T.Mukaiyama, Angew.Chem. 89, 858 (1977); Angew.Chem.,Int.Ed.Engl. 16, 817 (1977).
6) Instead of chlorides, the corresponding bromides can also be used. In case of zinc halides as the catalyst, room temperature is sufficient. The method in this case is essentially identical to that described by Paterson¹⁾, i.e., it corresponds to our method of α-tert-alkylation of esters using $ZnCl_2$²⁾.
7) It should be noted that many of the products are diastereomeric mixtures. No attempt was made to separate them.

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