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MANNICH REACTIONS OF ARYL-TRIALKYLSTANNANES USING PREFORMED DIALKYL-METHYLENEIMINIUM SALTS

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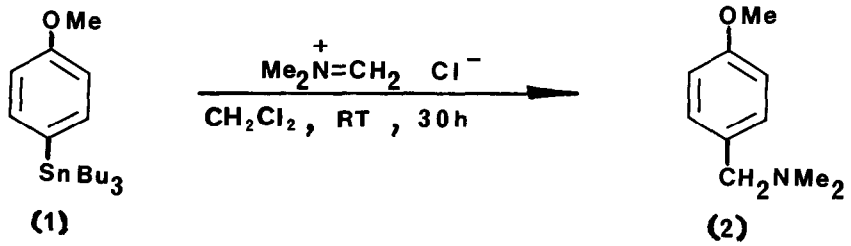
Summary: *Dialkyl-methyleneiminium salts react with aryl-tributyl- and aryl-trimethyl-stannanes to afford the corresponding N,N-dialkylaminomethyl- derivatives in good yields. The method can be used to obtain isomers that are not obtained by classical procedures.*

The Mannich reaction,[1] in which a labile proton is replaced by an α-aminoalkyl residue, is limited in its aromatic variation to nucleophilic systems. Thus heterocyclic compounds such as indoles[2] and pyrroles[3] have been widely studied as also have carbocyclic amines[4] and phenols.[5] Benzenoid compounds less reactive towards electrophiles than m-dimethoxybenzene[6] have not been reported to undergo Mannich reactions. The prediction[7] that the use of Eschenmoser salts[8] would improve the usefulness of the reactions has been verified recently in reactions of thiophenes and phenols. 2-Dialkylaminomethyl-thiophenes were obtained in good yields,[9] and phenols gave high regioselectivity (towards substitution at the 2-position) under mild phase transfer conditions.[10] The well established[11] increase in reactivity towards electrophilic addition-with-elimination reactions of certain aryl-alkylmetallic compounds prompted our study, some of the results of which we now report.

We did not observe any reaction when a solution of 4-methoxyphenyl-trimethylsilane in dichloromethane was stirred with an excess of N,N-dimethylmethyleneiminium chloride[12] over a prolonged period of time. The predictable increase in reactivity using 2-methoxyphenyl-trimethylsilane only resulted in the formation of N,N-dimethyl-2-methoxybenzylamine in <5% yield after 24h. However, when a solution of 4-methoxyphenyl tributystannane (1) in dichloromethane was stirred with N,N-dimethylmethyleneiminium chloride at room temperature the salt slowly dissolved and after about 30h we isolated N,N-dimethyl-4-methoxybenzylamine (2) in 70% yield.



(1) (2)

The generality of the above reaction and its use in carrying out Mannich reactions in the absence of electron releasing substituents is shown by the examples reported in the **TABLE** which also includes an example derived from methylenepiperidinium chloride. Reactions of the corresponding iodides, prepared from the aminals by interaction with iodotrimethyl silane[8c] gave in our hands lower yields than those reported in the **TABLE.**

TABLE

Reactions of Arylstannanes with Eschenmoser Salts ($[R_2N{=}CH_2]^+ \ Cl^-$)[@]

$$Ar\text{-}SnR_3 + [R_2N{=}CH_2]^+ \ Cl^- \longrightarrow Ar\text{-}CH_2NR_2 + R_3SnCl$$

iminium salt R_2 =	aromatic residue	alkyltin residue	solvent	conditions	yield‡ %
Me_2	phenyl-	$-SnMe_3$	CH_2Cl_2	24h reflux	65
Me_2	1-naphthyl-	$-SnBu_3$	CH_2Cl_2	24h reflux	66
Me_2	o-tolyl-	$-SnBu_3$	CH_2Cl_2	48h reflux	51
Me_2	m-tolyl-	$-SnBu_3$	CH_2Cl_2	48h reflux	60
Me_2	m-tolyl-	$-SnBu_3$	CH_3CN	4h reflux	39
Me_2	p-tolyl-	$-SnBu_3$	CH_2Cl_2	24h reflux	67
Me_2	o-anisyl-	$-SnBu_3$	CH_2Cl_2	15h reflux	70
Me_2	p-anisyl-	$-SnBu_3$	CH_2Cl_2	3 days RT	75
Me_2	p-anisyl-	$-SnBu_3$	CH_2Cl_2	15h reflux	70
Me_2	p-anisyl-	$-SnMe_3$	CH_2Cl_2	21h RT *	71
Me_2	3-thienyl-	$-SnMe_3$	CH_2Cl_2	60h RT	66
Me_2	p-thp-oxy-phenyl†	$-SnMe_3$	CH_2Cl_2	15h reflux	50
Me_2	p-phenylene-bis-	$-SnBu_3$	CH_3CN	48h reflux	58$
$(-CH_2-)_5$	o-anisyl-	$-SnBu_3$	CH_2Cl_2	24h reflux	57

@ Reactions carried out using $R_2N\text{-}CH_2\text{-}NR_2$: $ArSnR_3$ = 3 : 2.

‡ Yields not optimised.

* Reaction preceeded by 3h at -20°.

† thp = 2-tetrahydropyranyl.

$ ratio of $(Me_2N)_2CH_2$: p-$C_6H_4(SnBu_3)_2$ = 6:1;
product p-$C_6H_4(CH_2NMe_2)_2$.

Although the yields reported in the **TABLE** are similar for the butyl- and methyl-stannanes we were predjudiced initially to conclude that the reactions of the aryl trimethylstannanes proceed at faster rates than those of the aryl tributylstannanes. This predjudice undoubtedly arises from the more frequent use of aryl trimethylstannanes in electrophilic

addition-with-elimination reactions not withstanding the greater cost of trimethyl chlorostannane as compared with tributyl chlorostannane. We have carried out a series of competition reactions in order to obtain more information on this point.

A reaction in which N,N-dimethylmethyleneiminium chloride in dichloromethane was allowed to compete for a large excess of equimolar amounts of phenyl trimethylstannane and m-tolyl tributylstannane resulted in the formation of N,N-dimethylbenzylamine and N,N,3-trimethylbenzylamine in the ratio 2 : 8. In a similar reaction using phenyl tributylstannane and m-tolyl trimethylstannane the expected products were obtained in the ratio 2 : 5. It is clear from these results that there is no great advantage in using the aryl trimethylstannane, indeed the results might suggest that the transition state leading to the Wheland intermediate occurs at a later stage than in some other electrophilic destannylation reactions and that a greater relief of steric strain obtains using the aryl tributylstannanes. We also investigated the possible acceleration caused by an ortho- substituent by carrying out a reaction using o- and p-tolyl tributylstannanes as the competing pair. Remarkably, the presence of the ortho-methyl group does not cause an increase in the relative rate: the p-methyl : o-methyl isomer ratio was 8.5 : 1.5. It is evident that kinetic measurements should be made in order to evaluate relative reactivities accurately.

A significant effect due to the presence of an ortho-oxygen function was established by the use of o-methoxyphenyl- and p-methoxyphenyl- tributylstannane in a competition reaction which gave an o- : p- ratio of 6:4. We suggest that the electrophile may co-ordinate with the methoxy-group prior to attack at the nucleophilic centre and hence reaction is more favourable in the case of the o-methoxyphenyl tributylstannane.

That aminoalkyl-destannylation reactions can be used to achieve unusual regiospecificity was established by carrying out a reaction of 3-thienyl trimethylstannane (3) (prepared from 3-thienyl-lithium and chlorotrimethylstannane) with N,N-dimethyliminium chloride which afforded 3-N,N-dimethylaminomethylthiophene (4) in 66% yield. 3-Substituted thiophenes are most conveniently distinguished from their regio-isomers by ^{13}C nmr spectroscopy.[13] Thus 2-N,N-dimethylaminomethyl thiophene showed the following resonances [δ_C= 142.4(s), 126.4(d), 125.9(d), 125.0(d), 58.3(t), and 45.0(q) ppm], while 3-N,N-dimethylaminomethylthiophene showed resonances at δ_C= 139.7(s), 128.5(d), 125.4(d), 122.5(d), 58.8(t), and 45.2(q) ppm.

(3) (4)

Similarly, a reaction of N,N-dimethylmethyleneiminium chloride with p-tetrahydropyranyloxy-phenyl trimethyl-stannane gave, after the normal work-up, p-N,N-dimethylaminomethyl phenol in 50% yield. The reactions reported show that electrophilic dialkylaminomethyl-destannylation reactions proceed with useful regiospecificity. Our further studies are aimed at exploiting the regiochemical advantage.

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