Salts of acyl halides and 3,5-di-*tert*-butyl-4-hydroxy-N,N-dimethylbenzylamine in benzylation reactions

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The interaction of 3,5-di-*tert*-butyl-4-hydroxy-N,N-dimethylbenzylamine with various acyl halides has been studied. The N-acyl quaternary ammonium salts obtained can be used to introduce a sterically hindered phenol fragment into organic compounds containing an active methylene group.

Key words: 3,5-di-*tert*-butyl-4-hydroxy-N,N-dimethylbenzylamine, Mannich base, benzylation, pyridinium salt.

Among the benzylating agents which are used to introduce sterically hindered phenol fragments into various organic compounds, 3,5-di-*tert*-butyl-4-hydroxy-N,N-dimethylbenzylamine (**1**) is the most promising due to its stability and accessibility. The high thermal stability of Mannich base **1** (E_a = 134.74 kJ mol^{-1}, $\ln K_0$ = 27.10) requires severe conditions for benzylation that results in resinification of the reaction mixtures and the occurrence of secondary processes involving dimerization of the intermediate 2,6-di-*tert*-butylmethylenequinone. Thus, the possibility of using **1** as a benzylating agent is closely related to its activation.

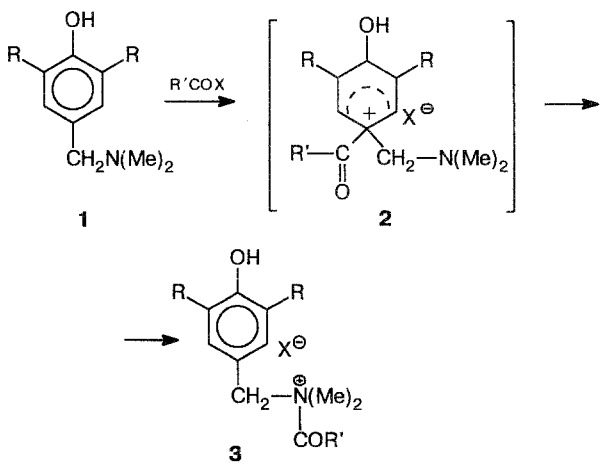
Dialkylbenzylamines are known[1] to interact with benzoyl and acetyl halides to give the corresponding benzyl halide and dialkylamides. Ammonium salt of the type $[RCON^+(CH_3)_2CH_2Ph]X^-$ has been proposed as an intermediate in this reaction. It may be expected that phenolic Mannich base **1** will also form an analogous ammonium salt, whose activity in benzylation reactions might be higher than that of original base **1**.

The purpose of the present work was to investigate the possibility of the formation of ammonium salts from **1** and acyl halides and to use such salts for the benzylation of compounds with an active methylene group. The following acyl halides were used: acetyl chloride, acetyl bromide, benzoyl chloride, and *p*-toluenesulfonyl chloride.

The reactions were carried out by adding the acyl halide to a solution of **1** in dry DMF, acetone, or acetonitrile at room temperature. The process is exothermic, and an intense violet color (green in transmitted light), which rapidly changes to pale yellow, appears. The following compounds were identified in the reaction mixtures by TLC (Silufol, ether : hexane = 1 : 5): 3,3′,5,5′-tetra-*tert*-butylstilbenequinone, di(3,5-di-*tert*-butyl-4-hydroxyphenyl)methane, and symmetric di(3,5-di-*tert*-butyl-4-hydroxyphenyl)ethylene. Besides, a significant amount of an unidentified compound was defected.

A white voluminous precipitate forms when the reaction of **1** with the acyl halides was carried out in dry ether, benzene, or hexane. Its chromatographic and chemical properties are identical to those of the aforementioned product formed when the reaction was carried out in acetone, acetonitrile, or DMF.

The observed course of the reactions of the acyl halides with **1** suggests the following preliminary conclusion: the reaction apparently involves the intermediate formation of an arenonium cation (**2**) (the apperance of the rapidly vanishing violet color), which is rapidly converted to an ammonium salt (**3**).



1 **2** **3**

R = CMe_3

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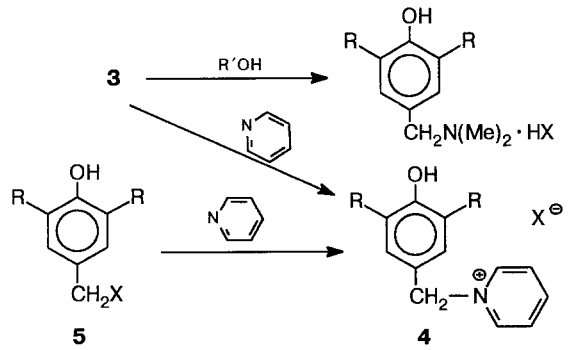
An attempt to isolate and identify ammonium salt **3** by elemental analysis, NMR spectroscopy, and IR spectroscopy failed. During filtration and drying, it was transformed into the hydrochloride of original Mannich base **1**. Similar results were obtained when alcohols were added to the reaction mixture.

The addition of equivalent amounts of pyridine to the reaction mixture resulted in the quantitative formation of a pyridinium salt of type **4**. We also note that the interaction of **3** with pyridine is a convenient practical method for obtaining a very effective benzylating agent,[2] viz. pyridinium salt **4**:

Acid halide	AcCl	AcBr	BzCl	TsCl
Yield of **4** (%)	95	93	95	72

The method is even more promising, since it makes it possible to obtain **4** in a crystalline form by consecutively mixing **1**, RCOX, and pyridine.



Pyridinium salt **4** can be obtained quantitatively[2] by reacting pyridine with benzyl halide **5**, which may also appear[1] as a result of a conversion of ammonium salt **3**.

The possibility of the conversion of **3** into halide **5** is governed mainly by the nature of the counterion X^-. This is evident from a comparison of the results of the reactions of **1** with AcCl and AcBr in hexane. Salt **3** is insoluble in hexane and can easily be separated from the benzyl halide by filtration, permitting the determination of the percentage of **3** converted into **5**. The yields of benzyl halides **5** and ammonium salts **3** were calculated from the yield of the pyridinium salt of type **4** isolated. It was found that in the case of acetyl chloride, the extent of the conversion of **1** into salt **3** is 75 %, while the yield of **3** is only 43 % when acetyl bromide is used. Accordingly, the hexane solution contains 17 % benzyl chloride **5** in the former case, while 34 % benzyl bromide **5** forms in the reaction of **1** with acetyl bromide (Table 1). Since the formation of **4** from **5** proceeds in the solid state, this must influence the yield of **4**. For this reason, the reaction was carried out in an homogeneous medium — in an acetone solution. As is seen from the data in Table 1, this dependence holds.

Table 1. Yields of salt **3** and benzyl halide **5** in the reaction of Mannich base **1** with various acyl halides in hexane and acetone

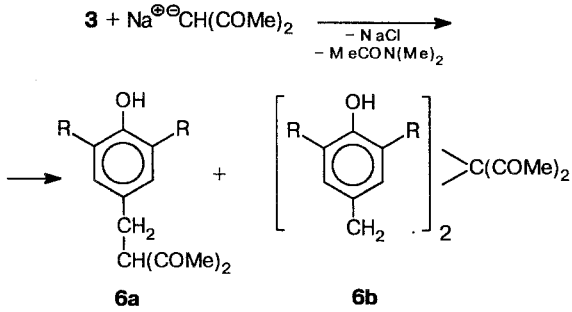
Acyl halide	Solvent	Yield (%)	
		3	**5**
CH_3COCl	Hexane	75	17
	Acetone	95	2
CH_3COBr	Hexane	43.5	34
	Acetone	63	29
C_6H_5COCl	Acetone	77	10
p-$CH_3C_6H_4SO_2Cl$	Acetone	72	13

Thus, the interaction of **1** with acyl halides involves the initial formation of ammonium salt **3**, which, in contrast to other data,[1] is converted to only a small extent into benzyl halide **5**. The yield of **5** depends both on the nature of the halide and on the polarity of the solvent.

The results can be logically explained within the framework of the conception of hard and soft acids and bases. For the benzyl cation the hardness of the bases diminishes along the series[3]:

$$I^- > HO^- > C_6H_5^- > Cl^- > Br^- > NH_2^- > CH_3^- > HS^-$$

On the basis of this series similar conversions should be expected for **3** with a carbanion (particularly, ^-CHXY) as a counterion. This was, in fact, observed experimentally. The addition of an acetonitrile solution of an equivalent of sodium acetylacetonate to an acetone solution of ammonium salt **3** obtained from **1** and acetyl chloride gave NaCl and mono- and dibenzyl derivatives **6a** and **6b**.



Apparently, the formation of **6** is preceded by the exchange of the chloride anion in the ammonium salt for a $^-CH(COCH_3)_2$ anion. Preliminary formation of sodium acetylacetonate is not essential for the synthesis of **6a** and **6b**, and it is sufficient to add equivalent amounts of acetylacetone and NEt_3 in acetone to an

Table 2. Results of the interaction of compounds of the type CH_2XY with acylammonium salt **3** in the presence of triethylamine

CH_2XY	**6a**		**6b**	
	Yield (%)	Mp (°C)	Yield (%)	Mp (°C)
Acetylacetone	52	85—86	18	160—161
Ethyl acetoacetate	65	Oil	15	135—136
Dimethyl malonate	63	Oil	7	171—172
Dimedone	61	203—204	26	237—238
Barbituric acid	—	—	72	> 250
Diethyl N-acetylaminomalonate	91	134—135	—	—

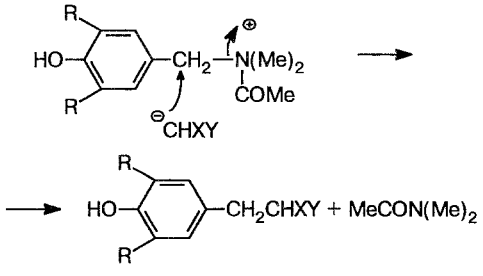
acetone solution of **3**. The precipitation of $NEt_3 \cdot HCl$ was observed. TLC analysis of the reaction mixture after storage for 1 h showed the presence of products containing one or two benzyl fragments.

Similar results (Table 2) were obtained for ethyl acetoacetate, dimethyl malonate, N-acetylaminomalonate, dimedone, and barbituric acid.

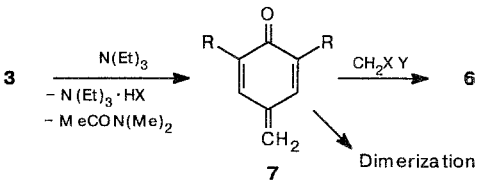
The spectral characteristics of compounds **6a** and **6b** are presented in Table 3.

The reaction of dimethyl malonate with a twofold excess of salt **3** gave a 54 % yield of the monosubstituted derivative and a 39 % yield of the disubstituted compound. The proportion of the disubstituted derivative depends on the **3** : CH_2XY ratio, the presence of the dibenzyl derivative in the reaction mixture being observed even at a 1 : 1 ratio. The benzylation of barbituric acid is an exception. In this case even when the ratio of reagents was equimolar, no monosubstituted derivative was detected in the reaction mixture and only disubstituted product was isolated. This is evidently due to the sharp difference between the acidities of barbituric acid itself and its 5-monobenzyl derivative.[4]

The mechanism of the reaction of **3** with CH_2XY can be interpreted as a molecular conversion of the ammonium salt involving the synchronous cleavage of a C—N bond and the formation of new C—C bond:



A quinometnide mechanism is also possible: NEt_3 reacts with salt **3** to generate a methylenequinone (**7**), which, being a strong benzylating agent,[5] is added to CH_2XY:



Apparently, both mechanisms are realized during the reaction. However, either of the mechanisms for the formation of **6** can predominate, depending on the nature of the cation in the salt M^+CHXY^- and the order of addition of the reagents.

Indeed, when NEt_3 is added to **3** before CH_2XY, the yield of **6** decreases, and a significant amount (up to 25%) of the corresponding stilbenequinone and diarylethylene, which are dimerization products[6] of methylenequinone **7**, appears in the reaction mixture. The methylenequinone mechanism probably becomes more preferable in this case. The use of harder sodium or potassium salts of CH_2XY makes the synchronous mechanism predominant.

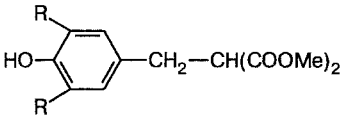
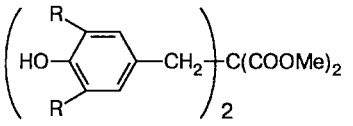
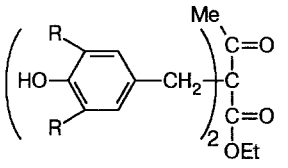
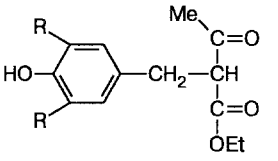
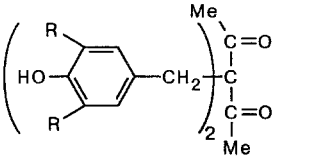
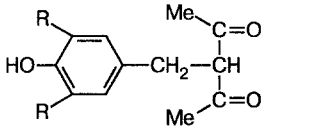
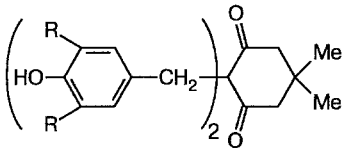
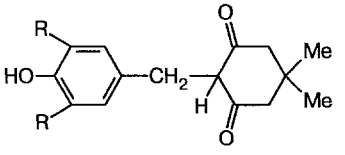
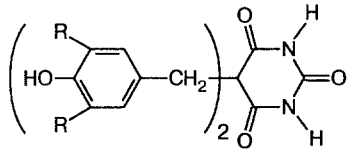
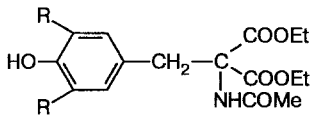
Experimental

The original 3,5-di-*tert*-butyl-4-hydroxy-N,N-dimethylbenzylamine and TsCl were recrystallized from hexane, mp 67—69 and 92—93°C, respectively, the acyl halides were purified by distillation, and the solvents were purified and dried in accordance with standard procedures.[7]

The NMR and IR spectra were recorded on Bruker P 80 WY (80.13 MHz) and Specord M80 (KBr) instruments, respectively. TLC was performed on Silufol plates; the thermal stability of original Mannich base **1** was determined on a Mettler TA 3000 derivatograph.

N-(3,5-Di-*tert*-butyl-4-hydroxybenzyl)pyridinium chloride (4). AcCl (0.72 mL, 10 mmol) was added to a solution of 2.63 g (10 mmol) of **1** in 20 mL of acetone. The mixture was held for 1 h at 20°C. Then 0.81 mL (10 mmol) of pyridine was added

Table 3. ^{1}H NMR shemical shifts of compounds obtained

Product	Structure	$CDCl_3$, δ
Dimethyl (3,5-di-*tert*-butyl-4-hydroxybenzyl)malonate		1.41 (18 H, *t*-Bu); 3.08 (2 H, CH_2); 3.68 (1 H, CH) 3.84 (t, 6 H, OCH_3); 5.84 (1 H, OH); 7.01 (2 H, Ph)
Dimethyl bis(3,5-di-*tert*-butyl-4-hydroxybenzyl)malonate		1.37 (36 H, *t*-Bu); 3.36 (6 H, CH_3); 3.53 (4 H, CH_2) 4.86 (2 H, OH); 7.19 (4 H, Ph)
Ethyl bis(3,5-di-*tert*-butyl-4-hydroxybenzyl)acetoacetate		1.40 (36 H, *t*-Bu) ; 1.14 (t, 3 H, $CH_2C\underline{H}_3$); 1.89 (3 H, OMe); 3.13 (4 H, CH_2) 4.07 (q, 2 H, $OC\underline{H}_2CH_3$); 5.88 (2 H, OH); 6.96 (4 H, Ph)
Ethyl (3,5-di-*tert*-butyl-4-hydroxybenzyl)acetoacetate		1.15 (t, 3 H, $CH_2C\underline{H}_3$); 1.41 (18 H, *t*-Bu); 2.15 (q, 3 H, Me); 3.03 (2 H, CH_2); 3.85 (1 H, CH); 4.10 (q, 2 H, $CH_2C\underline{H}_3$); 5.84 (1 H, OH); 7.01 (2 H, Ph)
Bis(3,5-di-*tert*-butyl-4-hydroxybenzyl)acetylacetone		1.42 (36 H, *t*-Bu); 2.79 (6 H, COMe); 3.25 (4 H, CH_2); 5.89 (2 H, OH); 6.93 (4 H, Ph)
(3,5-Di-*tert*-butyl-4-hydroxybenzyl)acetylacetone		1.36 (18 H, *t*-Bu); 1.70 (6 H, COMe); 3.03 (d, 2 H, CH_2); 3.73 (t, 1 H, CH); 4.85 (1 H, OH); 7.01 (2 H, Ph)
2,2-Bis(3,5-di-*tert*-butyl-4-hydroxybenzyl)-5,5-dimethylcyclohexane-1,3-dione		0.15 (6 H, Me); 1.38 (36 H, *t*-Bu); 1.77 (2 H, $COCH_2$) 3.16 (4 H, CH_2); 5.02 (2 H, OH); 6.85 (4 H, Ph)
2-(3,5-Di-*tert*-butyl-4-hydroxybenzyl)-5,5-dimethylcyclohexane-1,3-dione		1.10 (6 H, Me); 1.41 (18 H, *t*-Bu); 2.33 (2 H, $COCH_2$); 3.61 (d, 2 H, CH_2); 5.09 (1 H, OH); 5.84 (t, 1 H, CH); 6.99 (2 H, Ph)
5,5-Bis(3,5-di-*tert*-butyl-4-hydroxybenzyl)barbituric acid		1.38 (36 H, *t*-Bu); 3.34 (4 H, CH_2); 5.12 (2 H, OH); 6.72 (4 H, Ph); 7.42 (2H, NH)
Diethyl N-acetylamino-(3,5-di-*tert*-butyl-4-hydroxybenzyl)malonate		1.12 (t, 6 H, $CH_2C\underline{H}_3$); 1.41 (18 H, *t*-Bu); 2.15 (3 H, COMe); 3.50 (2 H, CH_2); 4.27 (q, 4 H, $C\underline{H}_2CH_3$); 5.93 (1 H, OH); 6.88 (2 H, Ph); 7.24 (1 H, NH).

and pyridinium salt **4** crystallized. The mixture was diluted with 100 mL of hexane, and the precipitate was filtered and dried to give **4** (3.1 g, 95 %), mp 227—229°C. Found (%): C, 71.99, H, 8.42. $C_{20}H_{28}ClNO$. Calculated (%): C, 71.94, H, 8.45. ^1H NMR ($CDCl_3$), δ: 1.42 (9 H, $C(CH_3)_3$), 5.73 (2 H, CH_2), 7.32 (1 H, OH), 8.11 (4 H, C_5H_5N), 8.58 (2 H, Ph), 9.03 (1 H, C_5H_5N).

Salts **4** were obtained similarly from benzoyl chloride (95 %) and TsCl (72 %); the yield of the corresponding pyridinium bromide from AcBr was 93%.

Dimethyl mono-and bis(3,5-di-*tert*-butyl-4-hydroxybenzyl)malonate (8a and 8b). AcCl (0.72 mL, 10 mmol) was added to a solution of 2.63 g (10 mmol) of **1** in 20 mL of acetone. The mixture was held for 1 h at 20°C, and a solution of 1.6 mL (0.01 mmol) of triethylamine and 1.3 mL (0.01 mmol) of dimethyl malonate in 20 mL of acetone was added. After 24 h at room temperature, the reaction mixture was poured into 300 mL of water and extracted with chloroform, and the extract was washed with water and concentrated *in vacuo* to 1/4 of its original volume. The products were isolated by flash chromatography on silica gel (50—150 mesh, chloroform : hexane, 1 : 1). 2.2 g (63 %) of dimethyl (3,5-di-*tert*-butyl-4-hydroxybenzyl)malonate (oil) and 0.4 g (7 %) of dimethyl bis(3,5-di-*tert*-butyl-4-hydroxybenzyl)malonate, mp 171—172°C, were obtained. Other compounds were obtained in a similar manner. The yields and physicochemical characteristics are listed in Tables **2** and **3**.

References

1. M. Tiffeneau and K. Fuhrer, *Bull. Soc. Chim. Fr.*, 1914, **15**, 162.
2. M.M.O. Movsoum-zade, D.Sc.Thesis, Institute of Petrochemical Processes, Academy of Sciences of Azerbaijan, Baku, 1985.
3. A. F. Bochkov, *Zh. Org. Khim.*, 1986, **22**, 2050 [*J. Org. Chem.*, 1986, **22** (Engl.Transl.)].
4. R. N. Nacheva, B.V.Chemishev, Z.A.Raikov, and D.N.Mikhailova, *Dokl. Bolg. Akad.Nauk*, 1981, **34**, 183.
5. A. A. Volod'kin and V. V. Ershov, *Usp. Khim.*, 1988, **57**, 595 [*Russ. Chem. Rev.*, 1988, **57** (Engl. Transl.)].
6. V.V.Ershov, G.A.Nikiforov, and A.A.Volod'kin, *Prostranstvenno-Zatrudnennye Phenoly* [*Hindered Phenols*], Khimiya, Moscow, 1972 (in Russian).
7. A.J.Gordon and R.A.Ford, *The Chemist's Companion*, J.Wiley & Sons, New-York-London-Sydney-Toronto, 1972.

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Reactions of benzamidoxime and its sodium salt with methyl esters of fluorinated acids

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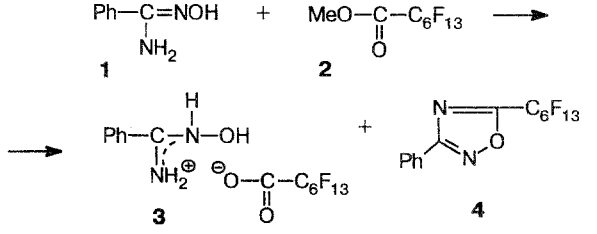
The reactions of benzamidoxime and its sodium salt with methyl esters of fluorinated acids at 20—100°C give 1,2,4-oxadiazoles or O-addition products.

Key words: benzamidoxime, methyl perfluoroheptanoate, α-methoxytetrafluoropropanoate, trifluoropyruvate, 1,2,4-oxadiazole.

Information on the reactions of fluorinated carbonyl compounds with arylamidoximes is scarce. The only know example is the reaction of perfluoroacyl chlorides with amidoximes, which gives oxadiazoles.[1] In this work, we investigated the interaction of benzamidoxime and its sodium salt with methyl esters of various fluorinated acids.

The reaction of benzamidoxime (**1**) with methyl perfluoroheptanoate (**2**) over the temperature range from 80°C to 110°C gave the salt of benzamidoxime and perfluoroheptanoic acid (**3**) and 5-perfluorohexyl-3-phenyl-1,2,4-oxadiazole (**4**).



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