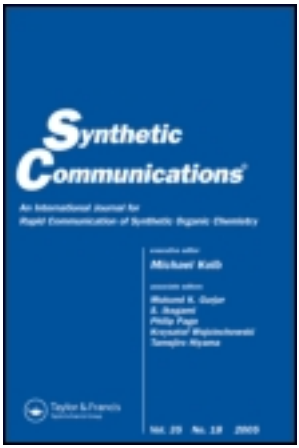

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Reactivity of Benzylic Acylammonium Chlorides. A Novel Method for the Synthesis of N-Phenacylamides

Necdet Coşkun [a] & Fatma Tirli [a]
[a] Department of Organic Chemistry, Uludag University, Bursa, 16059, TURKEY
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REACTIVITY OF BENZYLIC ACYLAMMONIUM CHLORIDES. A NOVEL METHOD FOR THE SYNTHESIS OF N-PHENACYLAMIDES.

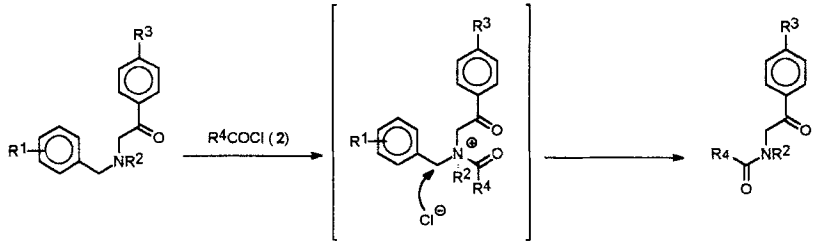
Necdet Coşkun* and Fatma Tirli
Department of Organic Chemistry, Uludağ University,
16059-Bursa.TURKEY

Abstract: Tertiary amines *1* reacted with acid chlorides *2* to give corresponding benzyl chlorides and N-phenacylamides *4*. Counterion in species *3* attacked preferentially the benzylic methylene. Effect of substituents in the benzyl group on the reactivity of acylammonium chlorides *3* was investigated.

N-Carbomethoxy-1,2- and -1,4-dihydropyridines have been prepared by the reaction of methyl chloroformate with pyridine using $NaBH_4$ as a reducing agent.[1] Fowler's reduction was investigated in the cases of 3-substituted pyridines by various hydride-transfer reducing agents in the presence of ethyl and benzyl chloroformate[2]. In natural product synthesis 1-acylpyridinium salts have found wide applicability in the preparation of alkaloids.[3,4] Kinetics of hydrolysis and aminolysis of 1-methoxycarbonylpyridinium ions have also been reported.[5]

* To whom correspondence should be addressed.

Method A.



1 **3** **4**

1a) $R^1 = H$ $R^2 = Me$ $R^3 = H$ ***1b***) $R^1 = 3,4(MeO)_2$ $R^2 = Me$ $R^3 = H$
1c) $R^1 = 2,3(MeO)_2$ $R^2 = Me$ $R^3 = H$ ***1d***) $R^1 = 3,4(OCH_2O)$ $R^2 = Me$ $R^3 = H$
1e) $R^1 = 3\text{-}MeO$ $R^2 = Me$ $R^3 = H$ ***1f***) $R^1 = H$ $R^2 = Me$ $R^3 = MeO$
1g) $R^1 = 3,4(MeO)_2$ $R^2 = Me$ $R^3 = MeO$ ***1h***) $R^1 = 3,4(OCH_2O)$ $R^2 = Me$ $R^3 = MeO$
1i) $R^1 = 3,4(MeO)_2$ $R^2 = PhCH_2$ $R^3 = H$ ***1j***) $R^1 = 3,4(OCH_2O)$ $R^2 = PhCH_2$ $R^3 = H$
1k) $R^1 = 3,4(MeO)_2$ $R^2 = 3,4(MeO)_2C_6H_3CH_2$ $R^3 = H$ ***1l***) $R^1 = 2\text{-}Cl$ $R^2 = Me$ $R^3 = H$
1m) $R^1 = 2\text{-}NO_2$ $R^2 = Me$ $R^3 = H$

Scheme 1.

It is well known that allylic or benzylic acyl ammonium salts, obtained by acylation of allylic or benzylic tertiary amines with alkyl chloroformates[6], are readily substituted with the counterion present in the reaction medium to afford the corresponding allyl or benzyl halides. Allylic acylammonium salt intermediates are employed in substitution reactions with Grignard reagents[6]. Furthermore, β-trimethylsilylethyl chloroformate was used for debenzylation of tertiary amines.[7] Although, some acylammonium salts have been reported to be stable[8], we have not found examples of benzylic acylammonium salts neither prepared nor used for the synthesis of compounds ***4***. N-Phenacylamides have been used in the synthesis of Cherylline and Latifine like structures. In the known procedure for the synthesis of mentioned amides benzaldehyde is reductively aminated with β-phenylethanolamine, and the resulting amine acylated and later oxidized with PCC.[9]

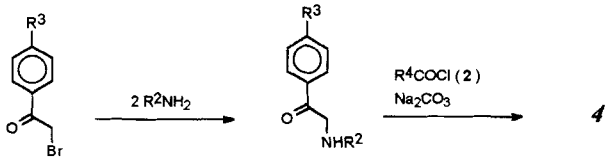
Recently we have reported the synthesis of N-benzyl-N-alkylphenylacetamides and their application to the preparation of 4-aryl-1,2,3,4-tetrahydroisoquinolin-3-ones.[10,11] As part of an ongoing effort in our laboratory to

develop a synthetic method for the construction of 1-benzoyl-1,2,3,4-tetrahydroisoquinolin-3-one framework, we have developed a new method for the synthesis of compounds ***4*** (***Method A***). Our strategy towards this objective is based on the in situ formation of the corresponding acylammonium chlorides ***3***, reaction of aminoketones ***1*** with acid chlorides ***2***, and their conversion to ***4*** in dichloroethane at reflux(***scheme 1***). Cleavage of the benzyl group depends on the substituents in the benzyl part of the aminoketones ***1***. It was clearly demonstrated that electron donating groups favored nitrogen-benzylic carbon bond scission, while in the case of unsubstituted benzyl or benzyl groups with electron withdrawing substituents the cleavage required stronger conditions and longer reaction times than in the other cases(***table 2***). Compounds ***1i,j*** were subjected to debenzylation with AcCl and we have observed that 3,4-dimethoxybenzyl and 3,4-methylendioxybenzyl groups cleave selectively. As a result we have obtained N-benzyl-N-phenacylacetamide which can be used in the synthesis of 1-acyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline after reduction of the ketone carbonyl with KBH_4. The preparations of N-methyl-N-phenacylacetamide and ***4e*** starting from ***1a*** and corresponding acid chloride were performed in acetonitrile in the presence of KI. N,N-Dialkylphenylacetamides have been isolated from the reaction mixture of ***1g*** when treated with 3,4-dimethoxyphenylacetyl and 3-methoxyphenylacetyl chlorides respectively. Their structures were proved by comparing them with those prepared by the method which have already been reported.[10,11]

In order to confirm the structure of compounds ***4***, we have synthesized them by a conventional route (***Method B***) by acylating N-alkylphenacylamine ***6*** with acid chloride ***2*** in a two-phase reaction using H_2O and $CHCl_3$ as solvent mixture and Na_2CO_3 as a base (***scheme 2***). The reason for the lower yields in ***method B*** is the reaction leading to the diphenacyl substituted amine. Although the problem was solved in these cases where volatile amines were used, using a large excess of the amine, the problem is inevitable when N-benzylphenacylamines are needed. In addition, all compounds prepared by ***method A*** were characterized by their IR, ^1H

NMR and MS spectra. The application of compounds ***4a-g*** for the synthesis of isoquinoline derivatives is underway.

Method B.



Scheme 2.

Table 1. N-Alkyl-N-phenacylamides

Pro-duct	Start. comp.	Yield of *4* (%) *A*	*B*	R^2	R^3	R^4	Molecular Formula	MS (70 eV) m/z (M+)
4a	*1g*	90	35	Me	MeO	3-$MeOC_6H_4CH_2$	$C_{19}H_{21}NO_4$ (327.367)	327
4b	*1b*	85	25	Me	H	3-$MeOC_6H_4CH_2$	$C_{18}H_{19}NO_3$ (297.337)	297
4c	*1b*	80	27	Me	H	3,4$(MeO)_2C_6H_4CH_2$	$C_{19}H_{21}NO_4$ (327.367)	327
4d	*1g*	82	30	Me	MeO	3,4$(MeO)_2C_6H_4CH_2$	$C_{20}H_{23}NO_5$ (357.387)	357
4e	*1a-e*(table 2)	31		Me	H	$PhCH_2$	$C_{17}H_{17}NO_2$ (267.317)	267
4f	*1f*[a],*h*88;92			Me	MeO	4-$MeOC_6H_4CH_2$	$C_{19}H_{21}NO_4$ (327.367)	327
4g	*1i,j* 90;78			$PhCH_2$	H	3-$MeOC_6H_4CH_2$	$C_{24}H_{23}NO_2$ (357.427)	357

[a]The reaction was performed in acetonitrile in the presence of KI.

Table 2. Preparation of ***4e*** and N-methyl-N-phenacylacetamide.

starting compound	reaction time	Solvent, reagent (substrate reagent ratio) catalyst, temperature	yield (%)
1a	3 h	dichloroethane, $PhCH_2COCl$(1:1), reflux	trace
1a	3 h	acetonitrile, $PhCH_2COCl$ (1:1) KI, reflux	90

Table 2. Continued

1a	16 h	dichloroethane, $PhCH_2COCl$(1:4), reflux	85
1b	3 h	dichloroethane, $PhCH_2COCl$(1:1), reflux	98
1c	3 h	dichloroethane, $PhCH_2COCl$(1:1), reflux	95
1d	4 h	dichloroethane, $PhCH_2COCl$(1:1), reflux	97
1e	6 h	dichloroethane, $PhCH_2COCl$(1:2), reflux	90
1l	18 h	dichloroethane, $PhCH_2COCl$(1:4), reflux	trace
1a	3 h	acetonitrile, AcCl (1:4) reflux	85
1a	18 h	reagent(AcCl) used as a solvent, reflux	95
1l	18 h	reagent(AcCl) used as a solvent, reflux	85
1m	18 h	reagent(AcCl) used as a solvent, reflux	82

Table 3. Compounds *4a-g*. IR and ^1H NMR data

	IR (neat)$\nu_{C=O}$	^1H NMR ($CDCl_3$) δ , TMS
4a	1642, 1696	3.07 (s, 3H, NCH_3), 3.81 (s, 5H, MeO and $NCOCH_2$), 3.86 (s, 3H, MeO), 4.80 (s, 2H, NCH_2CO), 6.82-6.97 (m, 4H, Ar), 7.20-7.28 (m, 2H, Ar), 7.83-7.95 (m,2H, Ar).
4b	1640, 1695	3.10 (s, 3H, NCH_3), 3.70-3.82 (m, 5H, MeO and $NCOCH_2$), 4.81 (s, 2H, NCH_2CO), 6.80-6.90 (m, 3H, Ar), 7.45-7.70 (m, 3H, Ar), 7.95 (m, 2H, Ar).
4c	1640, 1690	3.10 (s, 3H, NCH_3), 3.78 (s, 3H, MeO), 3.85 (s, 2H, $NCOCH_2$), 3.90 (s, 3H, MeO), 4.85 (s, 2H, NCH_2CO), 6.65-6.90 (m, 3H, Ar), 7.40-7.60 (m, 3H, Ar), 7.90-8.00(m, 2H, Ar)
4d	1638, 1690	3.10 (s, 3H, NCH_3), 3.78-3.95 (m, 11H,3x MeO and $NCOCH_2$), 4.80 (s, 2H, NCH_2CO), 6.60-7.00 (m, 5H, Ar), 7.85-7.95 (m, 2H, Ar).
4e	1640, 1690	3.08 (s, 3H, NCH_3), 3.8 (s, 2H, $NCOCH_2$), 4.85 (s, 2H, NCH_2CO), 7.20-7.60 (m, 8H, Ar), 7.80-7.95 (m, 2H, Ar).
4f	1640, 1690	
4g	1640, 1695	

EXPERIMENTAL SECTION

Starting aminoketones *1a-m* were prepared by method which is an improvement of our earlier procedure.[12] They were purified by recrystallization prior to use. Acid chlorides and phenacyl halides were purchased from Aldrich and were used without further purification. IR spectra of all

compounds prepared were recorded with MATTSON 1000 FTIR spectrometer. ^{1}H NMR spectra were observed with Gemini Varian 200 MHz instrument. Mass spectra were recorded with Hewlett-Packard GS-MS.

N-Alkyl-N-phenacylamides (4). General Procedure.- Method A: To a solution of aminoketon ***1*** maleat (1 mmol) in $CHCl_3$ (15 mL) water was added (20 mL) and basified to pH 10 with 25% NH_4OH. The layers were separated on a separation funnel. The water layer was extracted again with another portion of $CHCl_3$ (15 mL).The combined extracts were dried over anhydrous Na_2SO_4. After removal of the solvent the residue was dissolved in dichloroethane and acid chloride (1 mmol) diluted with dichloroethane was added dropwise to the mixture. The reaction mixture was refluxed for 3 to 6 hrs. The solvent was evaporated under reduced pressure and the residue was extracted with warm petroleum ether (3 X 10 mL), then with warm ether (3 X 10 mL). The ethereal extract contains mainly compound ***4***. Further purification of ***4*** was made by preparative TLC.

Method B: To a solution of 40% aq. $MeNH_2$ (10 mmol) in MeOH (25 mL) methanol solution of phenacyl bromide ***5*** (5 mmol) was added dropwise for 15-20 min. The reaction mixture was stirred for 50 min after the phenacyl bromide addition was completed. The solvent was evaporated on a rotary-evaporator, then water was added to the residue and extracted with $CHCl_3$ (2 X 20 mL). The combined extracts were washed with water (3 X 40 mL) then mixed with water (40 mL). After addition of solid Na_2CO_3 (5 mmol) to the vigorously stirred mixture, a solution of acid chloride (5 mmol) in chloroform was dropped within 15 min. The stirring was continued at room temperature for 60 min. The stirring was stopped then the organic layer was separated, washed three times with 5 % HCl (20 mL), and dried over anhydrous Na_2SO_4. After removal of the solvent the residue was chromatographed on silica gel(ether-petroleum ether 1:2).

N-Methyl-N-(4-methoxyphenacyl)-3-methoxyphenylacetamide (4a).- To a solution of aminoketone maleate ***1g*** (1 mmol, 0.387 g) in $CHCl_3$ (15 mL), water was added (20 mL) and basified to pH 10 with 25% NH_4OH. Organic phase was

separated and the water layer was extracted again with another portion of $CHCl_3$ (15 mL). The combined extracts were dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was dissolved in dry dichloroethane then 3-methoxyphenylacetyl chloride (1 mmol, 0.185 g) in dichloroethane was added to the mixture. The reaction mixture was refluxed for 3 hrs. The solvent was evaporated under reduced pressure and the residue was extracted with warm petroleum ether (3 X 10 mL) then with ether (3 X 10 mL). The mixture was chromatographed on silica gel (ether-petroleum ether 1:2). The compound was isolated as reddish oil and was identical with those obtained by method B.

N-Methyl-N-phenacylphenylacetamide (4e).- To a solution of aminoketone ***1b*** (1mmol, 0.239g) in acetonitrile, phenylacetylchloride was added (4 mmol, 0.618 g) dropwise. Powdered KI (2.5 mmol, 0.415g) was added and the reaction mixture was heated to reflux and stirred for 3 hrs. The reaction was stopped and the solvent evaporated on a rotary-evaporator. The residue was treated with water (20 mL) and extracted with $CHCl_3$ (2 X 15 mL). The combined extracts were washed with 15% NaOH (2 X 15 mL) 10% HCl (2 X 15 mL) and water (2 X 15 mL). The extract was dried over anhydrous Na_2SO_4, filtered and after removal of the solvent the crude amide was purified by TLC.

N-Methyl-N-phenacylacetamide.- The compound was prepared by method A starting from ***1a-e,l,m*** .Yields were between 80-95%. The compound was purified by recrystallization from ether, mp 68-69.3 °C. IR(KBr) $\nu_{C=O}$ 1630, 1696; ^1H NMR (200 MHz, $CDCl_3$) δ 2.15 (s, 3H, $NCOCH_3$), 3.10 (s, 3H, NCH_3), 4.82 (s, 2H, NCH_2CO), 7.40-7.65 (m, 3H, Ar), 7.95 (m, 2H, Ar). MS m/z 191 (M^+, 17.39), 120 (18.26), 105 (56.52), 86 (100), 77 (41.30), 51 (18.69).

N-(3,4-dimethoxybenzyl)-N-phenacylacetamide.- A solution of aminoketone maleate ***1k*** (1 mmol, 0.493 g) in 3 mL of AcCl was refluxed for 8 hrs. The reaction was stopped, and the excess of AcCl was evaporated. Water was added to

the residue (20 mL) and extracted with $CHCl_3$ (2 X 15 mL). The extract was washed with 10% HCl, 15% NaOH and water successively and dried over anhydrous Na_2SO_4. After removal of the solvent the crude product was purified by column chromatography (silica gel) using ether-petroleum ether as eluent. Yield 92%. IR(neat) $\nu_{C=O}$ 1640, 1695; MS m/z 327 (M^+).

N-Benzyl-N-phenacylacetamide.- The compound was prepared from ***1h*** and ***1i*** in a manner identical to the procedure for N-(3,4-dimethoxybenzyl)-N-phenacylacetamide outlined above. IR $\nu_{C=O}$ 1630, 1696; MS m/z 267 (M^+).

6,7-Dimethoxy-1-acetyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline.- To a stirred solution of N-(3,4-dimethoxybenzyl)-N-phenacylacetamide (0.5 mmol, 0.164 g) in methanol (15 mL) solid KBH_4 was added in portions within 15 min and the mixture was stirred for 4 hrs. The solvent was evaporated and the residue was treated with water and extracted with chloroform (2 X 10 mL). The extract was dried and filtered then treated with 95% H_2SO_4 (1 mL). The mixture was stirred at room temperature for 30 min then poured onto crushed ice (20 g). The organic layer was separated and washed with water and Na_2CO_3 solutions successively. The extract was dried over anhydrous Na_2SO_4, filtered and after removal of the solvent the crude acyltetrahydroisoquinoline was purified by TLC to afford 0.110 g oil. Yield 70%. IR $\nu_{C=O}$ 1640, MS m/z 311 (M^+, 100), 282 (3.44), 268 (13.79), 239 (41.37), 209 (67.24).

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