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SYNTHESIS OF N-SUBSTITUTED PIPERIDINES

Nucleophilic Displacement of Pyridine by Piperidine From *N*-Substituted Pyridinium Salts

Sayed M.M. Elshafie

Chemistry Department, Faculty of Sciences, University of Minia, Minia, Egypt

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N-substituted monocyclic, tricyclic, and pentacyclic-pyridinium salts were prepared by the interaction of pyrylium salts with variable amines. The *N*-substituted pyridinium obtained salts were reacted with piperidine by nucleophilic substitution to give *N*-substituted-piperidines.

Key words: Piperidines and Pyridinium Salts.

INTRODUCTION

In a previous paper we reported the preparation of C-substituted-pyrylium salts by Micheal's addition of ketones to chalcones using Lewis acid as a cyclodehydrating agent [1].

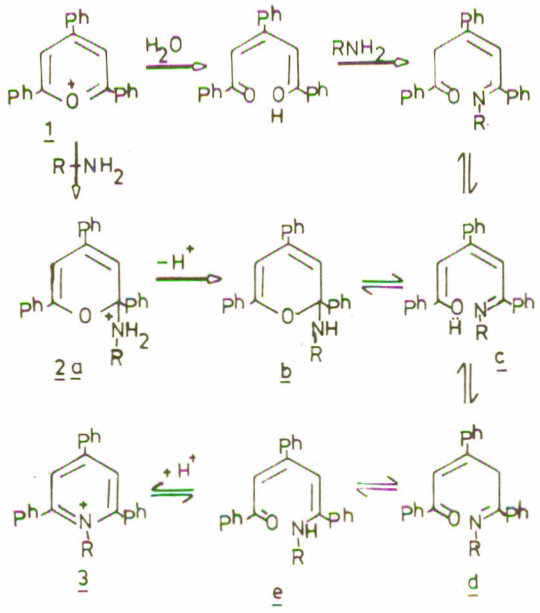
In the present paper we report the conversion of the previously prepared pyrylium into pyridinium salts. Several kinetic measurements were made for the determination of the reaction rate constant of the nucleophilic substitution reaction of *N*-substituted mono-, and tri-cyclic pyridinium cations by piperidine in chlorobenzene solvent [2, 3]. The proposed mechanism for nucleophilic substitution was a *trans*-aralphyl groups from the pyridinium salts to the piperidine nucleophile under pseudo-first order conditions, indicating that this nucleophilic displacements occur by S_N1 and/or S_N2 mechanism depending on the kind of the N-substituent groups. Also, this idea was previously confirmed by the preparation of fatty acids and fatty acid esters by nucleophilic substitutions of *N*-substituted-7-phenyl-5, 6, 8, 9-tetrahydro-dibenzo [c, h] acridinium trifluoromethane sulphonates [12] using sodium derivatives of other fatty acids esters as an easy method for preparation of other high molecular weight fatty acid esters [4].

In the present paper a synthetic proof for the previously reported *trans*-aralphyl mechanism [2, 3] involving the final transfer of substituent groups from *N*-substituted pyridinium salts to piperidine as a nucleophilic (Scheme 3) has been offered.

The mechanistic change over from pyrylium into pyridinium cations could be verified by the formation of a pseudo-base intermediate step. Pseudo-base formation could be rationalised either by the attack of water present as moisture in the reaction mixture or the amine at carbon 2, followed by deprotonation and ring-opening with the formation of the pseudo-base (2 a-e), and subsequent ring closure with the formation of the *N*-substituted pyridinium salt [3] (Scheme 1).

Susan and Balaban [5] isolated the tautomeric ketone-iminic-imino-enol intermediate (2 c, d, and e) by reacting 2, 4, 6-triphenylpyrylium perchlorate with methylamine in carbon-tetrachloride solvent.

Scheme 1



The fluoresence of pyrylium salt vanished when treated with methylamine with the concurent appearance of a deep red colour.

The red solution changed after a few minutes to a colourless solution of N-methyl-2, 4, 6-triphenylpyridinium perchlorate in carbon tetrachloride. The red colour was thought to be the charge transfer complex between the amine as donor and pyrylium cation as acceptor. This mechanism was confirmed by the author using butylamine in dichloromethane solvent [6] with 2, 4, 6-triphenyl-pyrylium perchlorate.

EXPERIMENTAL

IR spectra were measured in bromoform mull using Perkin Elmer 237 and NMR using Perkin Elmer R 12 (60 MHz) in $CDCl_3$ (using tetramethylsilane as internal reference). Melting points (uncorrected) were determined using Gallenkamp melting point apparatus. Evaporation refers to the removal of volatile material under diminished pressure. Whenever compounds were to be indentified, their identity was established by comparison of m.p., and TLC using reference samples prepared by usual methods for comparison of *N*-substituted-piperidines.

General method for the preparation of pyridinium cations (Table 1). The appropriate pyrylium cation (0.01 mole) was suspended in methanol (30 ml) and the required amine (0.015 mole) was added dropwise at room temperature while stirring for 3 hr. Diethyl ether was added to the previous reaction mixture with stirring for further one hr till complete precipitation of the pyridinium salt, The precipitate was filtered, and crystallised from *iso*propyl alcohol.

Preparation of piperidine derivatives (13). The appropriate pyridinium salt (0.1 mole) was suspended in dimethylformamide (100 ml). Then piperidine (0.15 mole) was added and the reaction mixture was refluxed for 6 hrs. The end of the reaction could be traced using TLC with pure reference samples of the corresponding derivative using chloroform as s solvent. At the end of the reaction the solvent was distilled. Addition of water and filtration led to the separation of pyridine derivative as the leaving group. The aqueous mother liquor, which contained unreacted piperidine and *N*-substituted piperidines, were benzoylated in ice-cold alkaline solution.

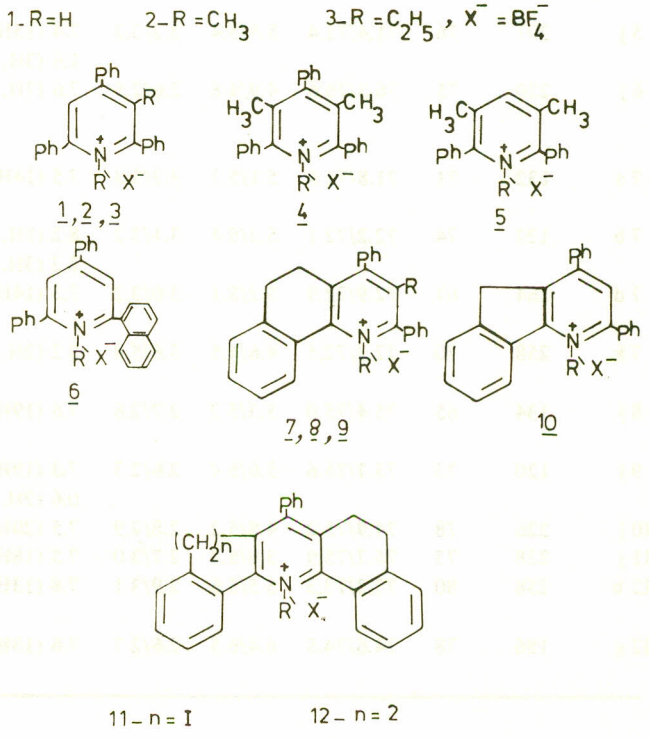
1-Benzoylpiperidine was filtered off and the mother liquor was extracted with diethyl ether (200 ml, twice), and then dried ($MgSO_4$). An ethereal solution of picric acid was added to the previously obtained *N*-substituted piperidine in dry diethyl ether with stirring for one hr. Evaporation of the ether solution yielded solid *N*-substituted piperidine picrate which could be crystallised from benzene-petroleum ether mixure (1:1) in the form of bright yellow needles (Table 2).

RESULTS AND DISCUSSION

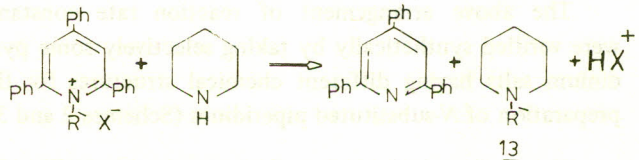
It has been found that polar solvents, preferably methyl alcohol, gave high yield and pure material than absolute ethyl alcohol or dipolar-aprotic solvents.

In another paper the author had reported the determination of the effect of different substituent groups introduced at carbons 2 to 6 of the heterocyclic pyridinium ring on the velocity of nucleophilic substitutions [2, 3] by piperidine with the following decreasing reaction rate constant series: 12 > 11 > 7 = 8 > 10 > 6 > 1 > 2 = 3 > 4 > 5. This could be attributed to the + I and the steric hindrance effects exerted by the aralphyl group substituents (Table 1, Scheme 2).

Scheme 2



Scheme 3



a – R` = Me b – R` = Et c – R` = *Iso*propyl
d – R` = Allyl e – R` = *Sec*-butyl f – R` = *n*-Pentyl
g – R` = *n*-Hexyl h – R` = *Cyclo*hexyl i – R` = Octyl
j – R` = Benzyl k – R` = 2-Pyridyl

Table 1. 1-Substituted pyridinium tetrafluoroborates [1-12].

Compd.	M.P. °C	Yield %	Elemental Analysis C/H/N			NMR (δ)	ν_{max} cm^{-1}
1 c	208	80	71.4/71.1	5.5/5.6	3.2/3.1	8.2 (2H, s), 7.8 (15H, s), 6.1 (1H, s), 2.3 (6H, m)	3010s, 1770s, 1620s, 1600m 1500s, 1480s, 1450m, 1140s 1050m.
1 e	172	74	71.9/71.6	5.8/5.6	3.1/3.0	8.1 (2H, s), 7.7 (15H, m), 4.5 (6H, m), 1.2 (3H, m)	1625s, 1600s, 1570s, 1290s 1280s, 760s.
1 f	246	70	72.3/72.0	6.0/6.2	3.0/3.1	8.1 (2H, s), 7.8 (15H, m), 4.5 (2H, t), 1.1 (9H, m)	1615s, 1590s, 1570s, 1280s
1 g	238	67	72.7/72.8	6.3/6.1	2.9/3.0	8.1 (2H, s), 7.6 (15H, m), 4.5 (2H, t), 1.2 (11H, m)	1600s, 1560m, 1530s, 1410s 1270s, 1130s, 1030s, 700s
1 h	188	83	72.8/72.3	6.9/6.3	2.9/2.9	8.0 (2H, s), 7.8 (15H, s), 5.2 (1H, s), 3.8 (10H, s)	1610s, 1600s, 1570s, 1490s 1470s, 1440m, 1130s, 1100m
1 i	155	78	73.4/73.5	6.7/6.7	2.8/2.8	8.1 (2H, s), 8.0 (15H, m), 4.5 (2H, t), 1.2 (15H, m)	1610s, 1590s, 1560s, 1540m 1410s, 1270s, 1190s, 1090s
2 j	118	70	74.5/74.8	5.2/5.7	2.8/2.9	7.5 (21H, m), 2.2 (5H, m)	1615s, 1600m, 1550s, 1180s 735s.
3 j	172	82	74.9/74.7	5.5/5.0	2.7/3.2	7.5 (21H, m), 5.7 (4H, m), 1.5 (3H, m)	1625s, 1600m, 1565m, 1495m 1025m, 1080m.
4 j	146	80	74.9/74.8	5.5/5.5	2.7/2.9	7.4 (20H, m), 5.5 (2H, m), 2.2 (6H, m)	1610s, 1495m, 1585s, 1450m 1070m, 1030m.
5 j	207	76	71.4/71.4	5.5/5.4	3.2/3.2	7.4 (15H, s), 7.2 (1H, s), 5.5 (2H, s), 1.8 (3H, s), 1.6 (3H, s)	3010s, 1620s, 1600s, 1420s 1140s, 1060m, 730s.
6 j	220	75	76.3/76.6	4.9/4.8	2.6/2.5	7.6 (7H, s), 7.2 (10H, m) 6.7 (2H, s), 5.8 (2H, s)	3010s, 1625s, 1590m, 1560s 1380s, 1250s, 1100s, 1050s 740s.
7 a	132	71	71.8/71.6	5.1/5.3	3.2/3.3	7.5 (14H, s), 5.8 (1H, m), 3.1 (4H, s), 2.7 (3H, s)	1616s, 1580s, 1150s, 1050m 890m.
7 b	122	74	72.2/72.1	5.3/5.4	3.1/3.2	8.2 (1H, s), 7.9 (14H, s), 5.3 (4H, s), 2.8 (2H, s), 2.2 (3H, m).	3010s, 1600s, 1560s, 1440m 1410s, 1210s, 1140s, 1020s.
7 d	164	67	72.9/72.9	5.2/5.1	3.0/3.2	7.3 (14H, s), 5.7 (1H, m), 4.9 (5H, m), 3.1 (4H, s)	3020s, 1630s, 1570s, 1500m, 1420s, 1170s, 1110s, 790s.
7 k	258	70	72.3/72.5	4.6/4.5	5.6/5.8	8.2 (2H, m), 7.2 (16H, m), 6.2 (1H, m), 2.7 (4H, s)	3010s, 1620s, 1600m, 1540s, 1440m, 1150s, 1050m.
8 j	134	65	75.4/75.0	5.3/5.2	2.7/2.6	7.6 (19H, m), 6.1 (2H, m), 2.9 (4H, m) 1.5 (3H, m)	1610s, 1590m, 1570m, 1500m 1060m, 1025m.
9 j	120	73	75.7/75.6	5.6/5.7	2.6/2.3	7.3 (19H, m), 6.0 (2H, m), 2.7 (4H, m), 2.1 (3H, m), 0.6 (2H, m).	1605s, 1585m, 1565m, 1450m
10 j	226	78	74.9/75.2	4.8/5.2	2.8/2.9	7.5 (20H, m), 6.1 (2H, m), 4.3 (2H, m)	1620s, 1590m, 1575m, 1500m
11 j	228	73	75.7/75.9	5.0/5.2	2.7/3.0	7.5 (18H, m), 6.4 (2H, m), 3.9 (2H, m), 2.8 (4H, m)	1615s, 1590m, 1500m
12 b	258	80	73.3/73.3	5.5/5.6	2.9/3.1	7.8 (13H, s), 6.1 (2H, m), 5.8 (8H, m), 1.8 (3H, s)	1600s, 1580s, 1410m, 1300m, 1200m, 1150s, 1050m.
12 g	186	78	74.6/74.5	6.4/6.5	2.6/2.7	7.6 (13H, s), 5.9 (2H, s), 5.4 (16H, m), 2.0 (3H, s)	2950s, 1600s, 1550s, 1420s, 1270s, 1030s, 770s.

The above arrangement of reaction rate constants were verified synthetically by taking selectively some pyridinium salts having different chemical structures for the preparation of *N*-substituted piperidines (Schemes 2 and 3).

Chemical and physical analysis was conducted on all selected pyridinium compounds, taking into consideration the case of the formation of the desired substituted-piperidine showing that the pentacyclic pyridinium cations possess the highest reaction velocity as compared to tricyclic and monocyclic-pyridinium salts.

Characteristic spectral details include in the ^{1}H NMR spectra a deshielded singlest for the 3– and 5– protons of the pyridinium ring; the chemical shifts for other protons are as expected. The IR spectra show the typical tetrafluoroborate peak, characteristic ring stretching bands at 1625-1605 and 1600-1585 cm^{-1}

Table 2. *N*-Substitute piperidine picrate derivatives [7-11]

Compd.	M.P. °C	Lit. M.P. °C	References	Yield %	Elemental Analysis [C/F]		
					C	H	N
13 a	226	226	6	60	43.9/43.7	4.9/4.8	17.1/17.3
13 b	171	170	6	73	45.6/45.8	5.3/5.6	16.4/16.7
13 c	152	151.5	7	70	47.2/47.4	5.6/5.7	15.7/15.8
13 d	75	73	8	81	47.5/47.8	5.1/5.5	15.8/15.4
13 e	98	100	9	75	48.6/48.8	5.9/5.7	15.1/15.6
13 f	107	105.5-107	6	67	50.0/50.2	6.3/6.8	14.6/14.9
13 g	104	106	6	74	51.2/51.7	6.5/6.6	14.1/14.2
13 h	128	128	9	80	51.5/51.6	6.1/6.2	14.1/14.0
13 i	72	70	10	73	53.5/53.8	7.0/7.2	13.1/13.4
13 j	176	179	8	82	53.5/53.7	5.0/5.4	13,9/14.3
13 k	139	138.5	10	42	49.1/48.9	4.3/4.7	17.9/17.8

CONCLUSION

This paper could be considered as a synthetic proof for *trans*aralphyl groups via N-C bond cession to piperidine during nucleophilic substitution reaction [2, 3].

Also, it presents an easy synthetic method for the preparation of differently *N*-substituted piperidines in high quantity and quality.

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