WITTIG REACTION OF AZABICYCLO-KETONES IN VARIOUS TWO-PHASE SYSTEMS

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Abstract- The present study is concerned with a comparison of variants of the phase transfer catalytic (PTC) Wittig reaction performed over azabicyclo-ketone systems, in attemt to extend the scope of the reaction and to learn whether an additional catalyst is required.

The Wittig reaction is commonly carried out in aprotic solvents in the presence of strong bases such as n-butyllithium, sodium hydride or sodamide. [1] The major advantage of the phase transfer method in Wittig reactions is increasing convenience of the reaction. Concentrated aqueous alkali is obviously easier to handle than n-butyllithium or sodium hydride and solvents such as benzene and dichloromethane are more readily removable after the reaction than DMSO. We have studied the reaction of the phosphonium salts: triphenylmethylphosphonium iodide; triphenylethylphosphonium iodide; triphenylbutylphosphonium bromide and cyclopropyltriphenylphosphonium bromide with azabicyclo-ketones: 2,4-diphenyl-3-azabicyclo[3.3.1]nonan-9-one 1; 2,4-bis(p-methoxyphenil)-3-azabicyclo[3.3.1]nonan-9-one 3; 7,9-diphenyl-8-azabicyclo[4.3.1]decan-10-one 9; 7,9-bis(p-methoxyphenyl)-8-azabicyclo[4.3.1]decan-10-one 11; 6,8-diphenyl-3-thia-7-azabicyclo-[3.3.1]nonan-9-one 17; 6,8-bis(p-methoxyphenyl)-3-thia-7-azabicyclo[3.3.1]nonan-9-one 19; their N-methyl derivatives 2,4,10,12,18,20; in the following base/solvent systems: solid potassium carbonate/benzene, solid potassium t-butoxide/benzene and 60% sodium hydroxide/dichoromethane.

Negative results were obtained in all cases when the phosphonium salt was triphenylethylphosphonium iodide, triphenylbutylphosphonium bromide or cyclopropyltriphenylphosphonium bromide, being attributable to steric impediment factors, in transition state (betaine and oxaphosphetane) which is implicated in the mechanism of the Wittig reaction. Meanwhile with triphenylmethylphosphonium iodide

the yields are generally acceptable, and the corresponding 9-methylene or 10-methylene derivatives: 5,6,7,8,13,14,15,16,21,22,23 and 24 were obtained (Scheme 1). In all cases, the yields were almost not dependent of the presence and the absence of an additional PTC catalyst (18-crown-6). We conclude that an additional catalyst for these reactions is not required. This conclusion is in line with the most recent ideas on catalyst operation in many PTC reactions in basic systems: substrate molecules are deprotonated at the interphase and the catalyst acts by carrying substrate anions from the interphase into the depth of the organic phase. [2-3] The deprotonation of phosphonium salts at the interphase yields neutral species that do not need the help of a PTC catalyst to diffuse into the organic layer. Apparently, the phosphonium salts which are reactants in this system are also effective as phase transfer agents. In the most strict sense then, these processes do not involve phase transfer catalysis.

The Tables I and II show our results for preparation of the methylene derivatives under various conditions. The Table I demonstrates that aqueous sodium hydroxide gave lower yields than solid potassium carbonate throughout. Best results, however, are achieved with solid potassium t-butoxide in benzene, independent of the carbonyl compound implicated. The 3-thia derivatives 21,22,23, 24 are obtained with lightly better performance, of course, as an influence of the sulfur atom in solubility of these compounds. On the other hand, Table II shows a little influence of the temperature in yields, in relation with the preparation of the same compounds at room temperature.

The ^{1}H-NMR analysis of the methylene derivatives showed marked constancy for the methylene group signal (C_9=CH_2 or C_{10}=CH_2), which is located at 4.80 ppm, the signal not being affected by the aromatic groups at C-2,C-4; C-7,C-9 or C-6,C-8; consequence of the cis-cis (and thus presumably diequatorial) orientation of the aryl groups follows from the equivalence of their signals and is in accordance with ^{13}C-NMR spectroscopic evidence determined by Eliell [4], for their initial ketones. The aromatic protons resound as a single multiplet in methylene derivatives with phenylic substituting, meanwhile when the aromatic group has p-methoxyphenyl nature, same protons appear as an AB system. The degradation suffered by one of the doublets when the nitrogen atom is substituted by a methyl group, becoming to a multiplet in 8,16,24, of course as a consequence of the no equivalence for rotation limitation of the aromatic rings, by interaction presented between the ortho-hydrogens of aromatic rings and the N-CH_3 substitution.

The substitution on the amine nitrogen in 3, 8 or 7 position in 3-azabicyclo-[3.3.1]nonane; 8-azabicyclo[4.3.1]decane and 3-thia-7-azabicyclo[3.3.1]nonane systems, respectively, does not affect chemical shift of the methylene signal, and this is related with the molecular conformation of these ketones: chair-chair for 3-azabicyclo[3.3.1]nonane systems 5,6,7,8; chair-boat (chair for the piperidine ring) for 8-azabicyclo[4.3.1]decane systems 13,14,15,16 and boat-chair (boat for the piperidine ring) for 3-thia-7-azabicyclo[3.3.1]nonane systems 21,22,23,24.[5-7] . As suggested by Zefirov [7] , bicyclo[3.3.1]nonane systems principally exist in one of the three following structures: chair-chair, chair-boat and boat-boat; structures free of tension of link angles. In the major part of cases the chair-chair conformation with light flattering in the rings, is favoured [8]. The flattering happens to minimize the transannular interactions among the endo-axial hydrogens and the C-3, C-7 positions. Meanwhile if the hydrogens are replaced by voluminous group, one of the rings will probably assume a boat conformation. The presence of the sulfur atom in 3 position affects in great extent to this arrangement, adopting boat conformation the piperidine ring for 3-thia-7-azabicyclo[3.3.1]nonane systems.

The infrared spectra reveal streching bands (C=C) at 1660 cm^{-1} and (H-C=C) at 3060 cm^{-1} . Presence of the Bohlmann band [9] in N-methyl derivatives 6,8,14,16, 22,24 attributed to substitution of the hydrogen by methyl group adopting equatorial disposition.

The simple preparative procedure and work-up may make this method worthwhile in certain cases although the yields are not generally excellent.

EXPERIMENTAL

The ketones 1,3,9,11 were prepared according to the literature [10], likewise their N-methyl derivatives 2,4,10,12 [6] and the 3-thia-ketones 17,19 and their N-methyl derivatives 18,20 [11] .

Preparation of C_9 and C_{10} methylene derivatives:

Procedure A: To a suspension of potassium carbonate (2.76 g, 20 mmol) and triphenylmethylphosphonium iodide (2.02 g, 10 mmol) in benzene (35 ml), an appropriate ketone 5 mmol was added. The mixture was stirred for 48 h at room temperature; 50 ml of ethyl ether was added to the mixture. The organic extracts are washed with water (50 ml) and dried on anhydrous magnesium sulfate. The solvent is evaporated under reduced pressure and the residue is purified by recrystallization.

Procedure B: An appropriate ketone(5 mmol) is added to a suspension of potassium t-butoxide (1.2 g, 10 mmol) and triphenylmethylphosphonium iodide (2.02 g, 10 mmol) in benzene (35 ml). The mixture was stirred for 48 h at room temperature. The mixture was treated as described above.

Procedure C: To a suspension of 60% sodium hydroxide (5 ml, 95 mmol) and triphenylmethylphosphonium iodide (2.02 g, 10 mmol) in dichloromethane (40 ml), an appropriate ketone (5 mmol) was added. The mixture was stirred for 48 h at room temperature. The reaction mixture was treated as described above.

2,4-Diphenyl-9-methylene-3-azabicyclo[3.3.1]nonane 5

mp 141°C (methanol); $C_{21}H_{23}N$ (289.4) calc: C, 87.12; H, 8.03; N, 4.83. found: C, 87.08; H, 8,07; N, 4.80. IR (KBr): ν = 3290, 3080, 2960, 2820, 1660 cm^{-1}; ^1H-NMR ($CDCl_3$) δ: 7.3 (m, 10H); 4.8 (s, 2H); 4,2 (d, 2H, J 2Hz); 2.4 (s, 2H); 1.5 ppm (m, 7H).

2,4-Diphenyl-3-methyl-9-methylene-3-azabicyclo[3.3.1]nonane 6

mp 128-129°C (methanol); $C_{22}H_{25}N$ (303.4) calc: C, 87.07; H, 8.30; N, 4.61. found: C, 87.05; H, 8.32; N, 4.63. IR (KBr): ν = 3080, 3010, 2960, 2790, 1660 cm^{-1}; ^1H-NMR ($CDCl_3$) δ: 7.4 (m, 10H); 4.8 (s, 2H); 3.6 (d, 2H, J 3Hz); 2.4 (s, 2H); 1.9 (s, 3H); 1.4 ppm (m, 6H).

2,4-Bis(p-methoxyphenyl)-9-methylene-3-azabicyclo[3.3.1]nonane 7

mp 146-148°C (methanol); $C_{23}H_{27}NO_2$ (349.3) calc: C, 79.04; H, 7.78; N, 4.00. found: C, 79.01; H, 7.80; N, 4.02. IR (KBr): ν = 3300, 3060, 2940, 2840, 1660 cm^{-1}; ^1H-NMR ($CDCl_3$) δ: 7.6 (d, 4H, J 9Hz); 6.8 (d, 4H, J 9Hz); 4.8 (s, 2H); 4.1 (d, 2H, J 2Hz); 3.7 (s, 6H); 2.4 (m, 2H); 1.6 (m, 6H); 1.0 ppm (s, 1H).

2,4-Bis(p-methoxyphenyl)-3-methyl-9-methylene-3-azabicyclo[3.3.1]nonane 8

mp 126-127°C (benzene); $C_{24}H_{29}NO_2$ (263.3) calc: C, 79.30; H, 8,04; N, 3.85. found: C, 79.26; H, 8.09; N, 3.85. IR (KBr): ν = 3060, 2980, 2900, 2790, 1660 cm^{-1}; ^1H-NMR ($CDCl_3$) δ: 7.3 (m, 4H); 6.9 (d, 4H, J 9Hz); 4.8 (s, 2H); 3.7 (s,6H); 3.0 (m, 2H); 2.2 (m, 2H); 1.9 (s, 3H); 1.4 ppm (m, 6H).

7,9-Diphenyl-10-methylene-8-azabicyclo[4.3.1]decane 13

mp 123-124°C (benzene); $C_{22}H_{25}N$ (303.4) calc: C, 86.99; H, 8,39; N, 4.61. found: C, 86.95; H, 8.41; N, 4.60.

IR (KBr): ν =3310, 3100, 2960, 2880, 1660 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ : 7.5 (m, 10H); 4.8 (s, 2H); 4.2 (d, 2H, J 2Hz); 2.8 (m, 2H); 2.1 (s, 1H); 1.2 ppm (m, 8H).

7,9-Diphenyl-8-methyl-10-methylene-8-azabicyclo[4.3.1]decane 14

mp 144-146°C (benzene); $C_{23}H_{27}N$ (317.4) calc: C, 87.01; H, 8.57; N, 4.41. found: C, 86.98; H, 8.60; N, 4.42.

IR (KBr): ν = 3060, 2980, 2860, 2790, 1660 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ : 7.5 (m, 10H); 4.8 (s, 2H); 4.0 (d, 2H, J 3Hz); 2.8 (m, 2H); 2.0 (s, 3H); 1.4 ppm (m, 8H).

7,9-Bis(p-methoxyphenyl)-10-methylene-8-azabicyclo[4.3.1]decane 15

mp 156-157°C (benzene); $C_{24}H_{29}NO_2$ (363.3) calc: C, 79.30; H, 8.04; N, 3.85. found: C, 79.27; H, 8.06; N, 3.83.

IR (KBr): ν = 3290, 3100, 2960, 2840, 1660 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 7.5 (d, 4H J 9Hz); 6.8 (d, 4H, J 9Hz); 4.8 (s, 2H); 4.0 (d, 2H, J 2Hz); 3.7 (s, 6H); 2.9 (m, 2H); 1.4 ppm (m, 9H).

7,9-Bis(p-methoxyphenyl)-8-methyl-10-methylene-8-azabicyclo[4.3.1]decane 16

mp 145-147°C (benzene); $C_{25}H_{31}NO_2$ (377.3) calc: C, 79.53; H, 8.27; N, 3.70. found: C, 79.50; H, 8.30; N, 3.69.

IR (KBr): ν = 3060, 2940, 2820, 2790, 1660 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ : 7.6 (m, 4H); 6.9 (d, 4H, J 9Hz); 4.8 (s, 2H); 3.7 (s, 8H); 3.4 (m, 2H); 2.9 (m, 2H); 2.0 (s, 3H); 1.5 ppm (m, 8H).

6,8-Diphenyl-9-methylene-3-thia-7-azabicyclo[3.3.1]nonane 21

mp 131-133°C (methanol); $C_{20}H_{21}NS$ (307.3) calc: C, 78.13; H, 6.68; N, 4.55. found: C, 78.10; H, 6.70; N, 4.52.

IR (KBr): ν = 3290, 3060, 2940, 2860, 1660 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ : 7.5 (m, 10H); 4.8 (s, 2H); 4.6 (d, 2H, J 2Hz); 3.0 (m, 6H); 1.5 ppm (s, 1H).

6,8-Diphenyl-7-methyl-9-methylene-3-thia-7-azabicyclo[3.3.1]nonane 22

mp 107-108°C (methanol); $C_{21}H_{23}NS$ (321.3) calc: C, 78.45; H, 7.21; N, 4.35. found: C, 78.41; H, 7.23; N, 4.35.

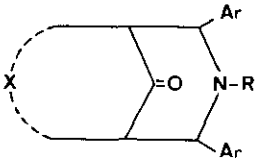
IR (KBr): ν = 3060, 2980, 2860, 2790, 1660 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ : 7.4 (m, 10H); 4.8 (s, 2H); 3.8 (d, 2H, J 4Hz); 2.9 (m, 6H); 1.8 ppm (s, 3H).

6,8-Bis(p-methoxyphenyl)-9-methylene-3-thia-7-azabicyclo[3.3.1]nonane 23

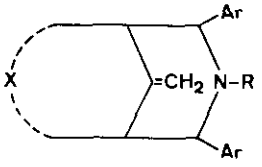
mp 136-137°C (methanol); $C_{22}H_{25}NO_2S$ (367.3) calc: C, 71.90; H, 6.85; N, 3.81; S, 8.72. found: C, 71.88; H, 6.88; N, 3.82; S, 8.71.

Scheme 1

Starting ketone



Reaction products



Comp. No.	X	R	Ar	Comp. No.	X	R	Ar
1	CH_2	H	C_6H_5	5	CH_2	H	C_6H_5
2	CH_2	CH_3	C_6H_5	6	CH_2	CH_3	C_6H_5
3	CH_2	H	p-$CH_3OC_6H_4$	7	CH_2	H	p-$CH_3OC_6H_4$
4	CH_2	CH_3	p-$CH_3OC_6H_4$	8	CH_2	CH_3	p-$CH_3OC_6H_4$
9	$(CH_2)_2$	H	C_6H_5	13	$(CH_2)_2$	H	C_6H_5
10	$(CH_2)_2$	CH_3	C_6H_5	14	$(CH_2)_2$	CH_3	C_6H_5
11	$(CH_2)_2$	H	p-$CH_3OC_6H_4$	15	$(CH_2)_2$	H	p-$CH_3OC_6H_4$
12	$(CH_2)_2$	CH_3	p-$CH_3OC_6H_4$	16	$(CH_2)_2$	CH_3	p-$CH_3OC_6H_4$
17	S	H	C_6H_5	21	S	H	C_6H_5
18	S	CH_3	C_6H_5	22	S	CH_3	C_6H_5
19	S	H	p-$CH_3OC_6H_4$	23	S	H	p-$CH_3OC_6H_4$
20	S	CH_3	p-$CH_3OC_6H_4$	24	S	CH_3	p-$CH_3OC_6H_4$

Table I: Reaction of triphenylmethylphosphonium iodide with carbonyl compounds, under stirring for 48 h at room temperature in the absence of an additional PTC catalyst.

Carbonyl compound	Base/solvent	Yield (%)
1	K_2CO_3/benzene	46
1	60% NaOH/CH_2Cl_2	34
1	KOtBu/benzene	49
2	K_2CO_3/benzene	50
2	KOtBu/benzene	56
3	K_2CO_3/benzene	43
3	60% NaOH/CH_2Cl_2	29
3	KOtBu/benzene	46
4	K_2CO_3/benzene	48
4	KOtBu/benzene	53
9	K_2CO_3/benzene	52
9	60% NaOH/CH_2Cl_2	40
9	KOtBu/benzene	59
10	K_2CO_3/benzene	51
10	60% NaOH/CH_2Cl_2	38
10	KOtBu/benzene	56
11	60% NaOH/CH_2Cl_2	48
11	KOtBu/benzene	62
12	K_2CO_3/benzene	51
12	60% NaOH/CH_2Cl_2	39
12	KOtBu/benzene	57
17	60% NaOH/CH_2Cl_2	44
17	KOtBu/benzene	65
18	K_2CO_3/benzene	56
18	KOtBu/benzene	71
19	K_2CO_3/benzene	53
19	60% NaOH/CH_2Cl_2	46
19	KOtBu/benzene	65
20	K_2CO_3/benzene	52
20	KOtBu/benzene	68

Table II: Reaction of triphenylmethylphosphonium iodide with carbonyl compounds, under stirring for 48 h with variation of temperature.

Carbonyl compound	Base/solvent	Temperature(°C)	Yield(%)
1	60% NaOH/CH_2Cl_2	40	40
1	KOtBu/benzene	60	46
1	KOtBu/benzene	80	48
3	K_2CO_3/benzene	60	45
3	KOtBu/benzene	80	48
9	60% NaOH/CH_2Cl_2	40	38
9	KOtBu/benzene	60	57
9	KOtBu/benzene	80	55
11	60% NaOH/CH_2Cl_2	40	45
11	KOtBu/benzene	80	65
12	K_2CO_3/benzene	60	49
12	60% NaOH/CH_2Cl_2	40	49
12	KOtBu/benzene	80	63
13	KOtBu/benzene	80	70
14	60% NaOH/CH_2Cl_2	40	47
14	KOtBu/benzene	60	63
14	KOtBu/benzene	80	67

IR (KBr): ν = 3290, 3080, 2960, 2840, 1660 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ : 7.4 (d, 4H, J 9Hz); 6.9 (d, 4H, J 9Hz); 4.8 (s, 2H); 3.7 (s, 6H); 3.3 (m, 2H); 2.8 (m, 6H); 1.6 ppm (s, 1H).

6,8-Bis(p-methoxyphenyl)-7-methyl-9-methylene-3-thia-7-azabicyclo[3.3.1]nonane 24

mp 122-123°C (ethanol); $C_{23}H_{27}NO_2S$ (381.3) calc: C, 72.40; H, 7.13; N, 3.67; S, 8.40. found: C, 72.37; H, 7.15; N, 3.68; S, 8.41.

IR (KBr): ν = 3060, 2940, 2860, 2780, 1660 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ : 7.5 (m, 4H); 6.8 (d, 4H, J 9Hz); 4.8 (s, 2H); 3.7 (s, 6H); 3.3 (m, 2H); 2.7 (m, 6H); 1.9 ppm (s, 3H).

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