Asian Journal of Chemistry Vol. 20, No. 2 (2008), 1373-1381

Reaction of 2-Phenyl- and 2-Methyl-cycloalkanones with PBr_5 and Influence of Substituent on the Addition of Bromine Atom

MUSTAFA CEYLAN*, MELIHA BURCU GÜRDERE and YAKUP BUDAK
Department of Chemistry, Faculty of Arts and Sciences
Gaziosmanpasa University, 60250 Tokat, Turkey
Fax: (90)(356)2521585; Tel: (90)(356)2521616
E-mail: mceylan@gop.edu.tr; ybudak@gop.edu.tr

The reactions of 2-phenylketones **1**, **4** and **12** with PBr_5 gave the α-brominated ketones as a regioselectivly and the α,α'-dibrominated ketones. But, the reactions of 2-methyl-ketones **7a-c** with PBr_5 gave only the α,α'-dibrominated ketones.

Key Words: Regioselectivity, α-Phenyl ketone, Methyl ketone, PBr_5.

INTRODUCTION

Cyclic vinyl halides have a large importance in the synthesis of organic compounds such as strained cyclic allenes[1-4] -alkynes[5] and vinyl silanes[6], *etc*. The main classical methods for preparing cyclic vinyl halides are dehydrohalogenation[7] of 1,2-dihalocycloalkanes and the reaction of cyclic ketones with PX_5[8-10]. Under the usual conditions, mixtures of isomers are formed from unsymmetrical ketones in the latter method. Hudrlik reported[11] that the treatment of 2-methylcyclohexanone with PCl_5 gave the mixture of 1-chloro-2-methylcyclohexene and 2-chloro-3-methyl-cyclohexene. Brown and co-workers reported[12] that the small-ring cyclic ketones react with PCl_5 to give the corresponding 1,1-dichlorocycloalkanes and of PBr_5 to give ketones brominated in the α-positions.

The regioselective bromination of unsymmetrical ketones has long attracted attention as a method to introduce functionality at the α-position. The preferred position of bromination with most brominating agents is usually at the more substituted carbon rather than at a methyl or less substituted carbon[13]. Sometimes complex mixtures including polybrominated products are obtained. One of the most well known procedures for the bromination of less substituted carbons such as methyl involves use of silyl enol ether generated from the kinetic enolate with LDA[14,15]. Furthermore, the 2-substitued ketones, especially, 2-phenyl ketones are used in

the synthesis of a variety of biologically interesting compounds[16]. According to the literature surveys, the reactions of 2-substitued cyclic ketones with PBr_5 were not investigated earlier. Therefore, we wish to investigate the reaction of 2-substituted-cyclic ketones with PBr_5 to reveal the side effect of substituents to these reactions.

EXPERIMENTAL

All the solvents were dried and distilled by standard procedures. Infrared spectra were obtained from films on NaCl plates or from solution in 0.1 mm cells on a Jasco FT/IR-430 spectrometer. ^1H and ^{13}C NMR spectra were recorded on 200 (50) MHz Varian spectrometers and reported in δ units with TMS as internal standart. All column chromatogrphy was performed on silica gel (60 mesh, Merck). The elemental analysis carried out with a CHNS-932 (LECO) analyzer.

General procedure for the reaction of 2-substituted ketones with PBr_5 and PCl_5: To a stirred solution of 2-substituted cycloalkanone, 1 mol equiv. in 50 mL of CCl_4 at room temperature was added either PBr_5 or PCl_5 1 mol equiv. and stirred for 16 h at room temperature. Then, the mixture was washed with water (2 × 50 mL) and dried over $MgSO_4$. Concentration in a rotatory evaporator gave the crude product which was purified on a silica gel column (40 g) or florocyl column (20 g) (*n*-hexane/$CHCl_3$, 8:2) to get the product as a colourless liquid.

2,5-Dibromo-2-phenylcyclopentanone (2): (Yield 10 %, colourless liquid). ^1H NMR (200 MHz, $CDCl_3$) δ = 7.34 (m, 5H), 5.34 (dd, *J* = 9.9 Hz, 3.3 MHz, 1H), 2.60 (m, 2H), 1.95 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 171.93, 140.24, 129.08 (2C), 128.74, 126.20 (2H), 82.14, 30.98, 29.98, 19.06. Anal. (%) calcd. for ($C_{11}H_{10}OBr_2$): C, 41.55; H, 3.17. Found: C, 41.78; H, 3.36.

5-Bromo-2-phenyl-2-cyclopent-1-enone (3): (Yield 34 %). ^1H NMR (200 MHz, $CDCl_3$) δ = 7.75 (m, 3H, aromatic and olefinic), 7.38 (m, 3H), 4.51 (dd, *J* = 6.6, 2.2 Hz, 1H), 3.19 (ddd, *J* = 20.24, 6.60, 3.19, 1H), 3.00 (dt, *J* = 20.24, 2.64, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 200.95, 155.82, 141.31, 131.20, 129.50, 129.02(2C), 127.50(2C), 42.99, 38.39. IR (CCl_4, cm^{-1}) 3080, 3020, 2940, 2830, 1720, 1490, 1455, 1430, 1120, 925, 690. Anal. (%) calcd. for ($C_{11}H_9OBr$): C, 55.72; H, 3.83. Found: C, 55.48; H, 3.99.

(2S,6R)-2-Bromo-6-phenylcyclohexanone(5): (Yield 38 %, colourless liquid). ^1H NMR (200 MHz, $CDCl_3$): δ = 7.37 (m, 5H), 4.79 (dd, 1H; *J* = 6.03 and 12.82), 2.75 (m, 1H), 2.11 (m, 2H), 1.88-1.45 (m, 4H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 203.45, 139.95, 130.74(2C), 129.24(2C), 129.15, 59.55, 58.45, 42.20, 37.64, 28.12. IR (liquid, cm^{-1}): 3106, 3080, 3029, 2953, 2876, 1727, 1600, 1497, 1191, 1063, 910, 808. Anal. (%) calcd. for ($C_{12}H_{13}OBr$): C, 56.94; H, 5.18. Found: C, 56.24; H, 5.36.

(2S,6S)-2-Bromo-6-phenylcyclohexanone (6): (Yield 18 %, colourless liquid). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.36 (m, 5H), 3.72 (dd, 1H; *J* = 5.12 and 12.45), 2.84 (m, 1H), 2.38-1.44 (m, 6H). ^{13}C NMR (50 MHz, $CDCl_3$, ppm): δ = 202.21, 144.54, 130.53(2C), 130.08, 129.56(2C), 63.87, 50.61, 35.40, 33.50, 27.99. IR (liquid, cm^{-1}): 3080, 3030, 2950, 2874, 1712, 1548, 1472, 1140, 1038, 796. Anal. (%) calcd. for ($C_{12}H_{13}OBr$): C, 56.94; H, 5.18. Found: C, 56.76; H, 5.48.

(2S,7S)-2-Bromo-7-phenylcycloheptanone (13 or 14): (Yield 32 %, colourless liquid). ^{1}H NMR (200 MHz, $CDCl_3$, ppm): δ = 7.27 (m, 5H), 3.73 (dd, 1H; *J* = 4.21 and 11.17 Hz), 2.69 (m, 1H), 2.52 (m, 2H), 2.09-1.32 (m, 6H). ^{13}C NMR (50 MHz, $CDCl_3$, ppm): δ = 214.97, 142.44, 130.47, 130.06, 129.86, 60.76, 44.31, 34.02, 31.98, 30.55, 27.32. IR (liquid, cm^{-1}): 3060, 3023, 2925, 2856, 1714, 1498, 1492, 1448, 1319, 1153, 696, 565. Anal. (%) calcd. for ($C_{13}H_{15}OBr$) : C, 58.44; H, 5.66. Found: C, 58.32; H, 5.78.

(2R,7S)-2-Bromo-7-phenylcycloheptanone (13 or 14): (Yield 18 %, colourless liquid). ^{1}H NMR (200 MHz, $CDCl_3$, ppm): δ = 7.34 (m, 5H), 4.28 (dd, 1H *J* = 3.02 and 11.82 Hz), 2.61 (m, 1H), 2.16-1.42 (m, 8H). ^{13}C NMR (50 MHz, $CDCl_3$, ppm): δ = 206.78, 141.59, 130.30, 129.99, 129.05, 54.32, 44.73, 36.68, 35.48, 34.02, 28.75. IR (liquid, cm^{-1}): 3060, 3029, 2925, 2856, 1702, 1492, 1448, 1128, 937, 757, 696.

(2R,6S)-2,6-Dibromo-2-methylcyclohexanone (20b or 21b): (Yield 47 %, colourless liquid). ^{1}H NMR (200 MHz, $CDCl_3$, ppm): δ = 5.56 (dd, 1H; *J* = 6.4 and 12.90 Hz), 2.64 (m, 1H), 2.44 (m, 1H), 2.19 (m, 2H), 1.89 (s, 3H), 1.85 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$, ppm): δ = 197.80, 66.88, 54.05, 45.32, 41.42, 30.82, 25.61. IR (liquid, cm^{-1}): 2929, 2863, 1727, 1668, 1544, 1444, 1299, 1195, 1130, 1070, 727, 667, 474. Anal. (%) calcd. for ($C_7H_{10}OBr_2$): C, 31.14; H, 3.73. Found: C, 31.32; H, 3.88.

(2R,6R)-2,6-Dibromo-2-methylcyclohexanone (18b or 19b): (Yield 24 %, colourless liquid). ^{1}H NMR (200 MHz, $CDCl_3$, ppm): δ = 5.03 (dd, 1H; *J* = 5.05 and 7.75 Hz), 2.40 (m, 1H), 2.20 (m, 1H), 2.04 (m, 1H), 1.58 (m, 1H), 1.42 (s, 3H), 1.34 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$, ppm): δ = 213.45, 70.17, 55.27, 45.64, 38.74, 28.78, 24.03. IR (liquid, cm^{-1}): 2923, 2854, 1733, 1454, 1290, 1189, 1130, 1070, 962, 862, 667, 538, 404.

6-Bromo-2-methylcyclohex-2-enone (20b): (Yield 8.50 %, colourless liquid). ^{1}H NMR (200 MHz, $CDCl_3$, ppm) δ = 7.52 (dd, 1H; *J* = 3.44 and 6.03), 4.33 (m, 1H), 2.28 (m, 2H), 2.16 (s, 3H), 2.03 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$, ppm): δ = 198.34, 132.79, 130.77, 61.56, 40.16, 38.74, 33.21. IR (liquid, cm^{-1}): 2942, 2863, 1727, 1444, 1380, 1299, 1120, 1070, 921, 727, 867, 668, 603. Anal. (%) calcd. for (C_7H_9OBr): C, 44.47; H, 4.80. Found: C, 44.36; H, 4.88.

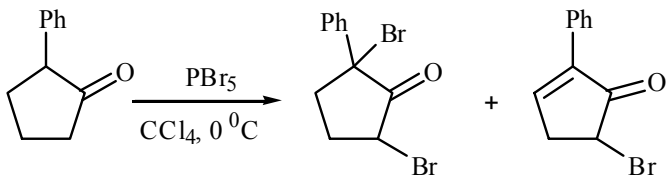
(2R,7R)-2,7-Dibromo-2-methylcycloheptanone and (2R,7S)-2,7-dibromo-2-methyl-cycloheptanone (18c and 19c): (Combined yield 60%,

colourless liquid). ^{1}H NMR (200 MHz, $CDCl_3$, ppm): δ = 5.12 (dd, 1H; *J* = 2.95 and 11.83 Hz), 4.71 (dd, 1H; *J* = 4.78 and 10.27 Hz), 2.49 (m, 4H), 2.33 (m, 4H), 1.92 (m, 4H), 1.86 (s, 3H), 1.78 (s, 3H), 1.49 (m, 2H), 1.14 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$, ppm): δ = 208.54, 207.98, 68.41, 65.28, 52.07, 51.76, 44.27, 43.62, 40.69, 38.90, 36.99, 31.82, 30.88, 29.94, 28.16, 26.66. IR (liquid, cm^{-1}): 2929, 2863, 1733, 1668, 1544, 1444, 1189, 1120, 1070, 921, 862, 782, 727, 667, 603, 474.

RESULTS AND DISCUSSION

We assume that the reactions of 2-substituted ketones **1, 2, 3** and **7a-c** with PBr_5 would give *geminal*-dibromides derived from carbonyl group or bromination of the less substituted carbons. The treatment of ketone **1** with PBr_5 in CCl_4 at room temperature gave dibromo ketone **2** and α,β-unsaturataed brome ketone **3** (**Scheme-I**). The formation of **2** can be reasonably explained by the haloform-type addition of molecular bromine, formed in the medium of reaction, to the ketone **1**. It is clear that α,β-unsaturated bromo ketone **3** is formed by elimination of HBr from dibromo ketone **2**.

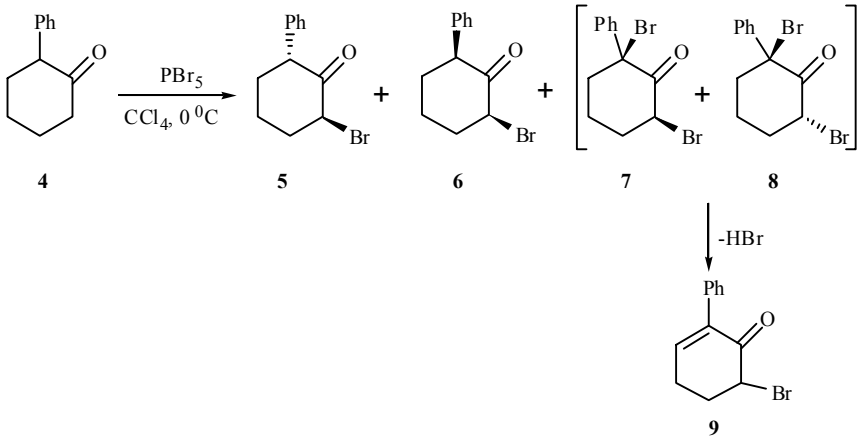
The structure of product **3** was determined by spectral data. The intersting feature of its ^{1}H NMR spectra is the AB system arising from the methylene protons (-CH_2-) which are bonded to an asymmetric carbon atom. The A-part (down field resonance) and the B-part of the AB system give a doublet of doublet of doublet (*J* = 20.2, 6.6 and 2.8 Hz) and a triplet of doublet (*J* = 20.2 and 2.8 Hz) at 3.19 and 3.00 ppm, respectively.



1 **2** **3**

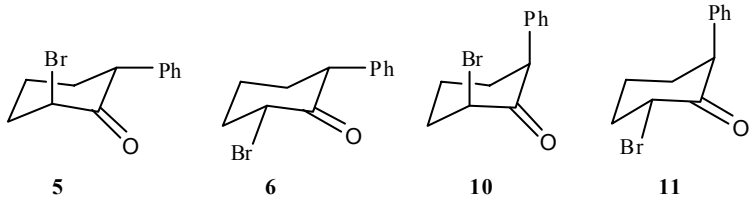
Scheme-I

2-Phenylcyclohexanone **4** reacted with PBr_5 in CCl_4 at room temperature to give a mixture of products which immediately eliminates HBr at room temperature (**Scheme-II**). Three ketones were observed from the NMR spectra of mixture (^{13}C NMR shifts: at 202.21, 203.45 and 198.75 ppm). According to the data, one of them is α,β-unsaturated ketone **9** (β carbon of α,β-unsaturated system resonates at 152.48 ppm) and the others are α-brominated diastereomers **5** and **6**. However, four products may be formed according to reaction of PBr_5. Two of them are α-brominated ketones **5** and **6** and the others are α,α'-dibrominated ketones **7** and **8**.



Scheme-II

The formation of the α,β-unsaturated ketone **9** shows that the compounds **7** and **8** may occur in the reaction medium, because compound **9** can be only derived from HBr elimination of the compound **7** and **8**. We separated compound **5** and **6** (yield: 38 and 18 %, respectively) on a silica gel column, but not α,β-unsaturated ketone **9**. As known α,β-unsaturated ketones are very stable. But, the bromine atom is removed easily on the silica gel column since compound **9** has a bromine atom at the α' position to carbonyl group. So, **9** has been exhibiting unstable situation. However, α-brominated products (**5** and **6**) may have four different conformational structures, which are **5, 6, 10** and **11** (**Scheme-III**).



Scheme-III

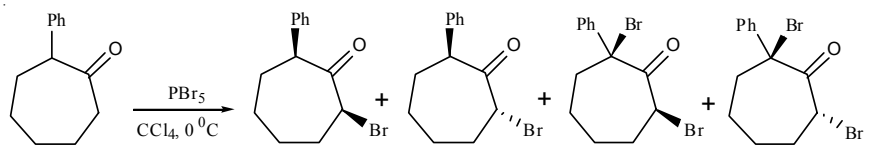
The structures of **5** and **6** were determined on the basis of spectral data. The ^{1}H NMR spectrum of **5** showed that the proton neighbouring to bromine at 4.79 ppm arises as a doublet of doublet (J = 6.0 and 12.8 Hz) and of other isomer **6** at 3.72 ppm as a doublet of doublet (J = 5.1 and 12.8 Hz). In addition to the proton NMR, ^{13}C NMR spectra showed 10 lines for each isomer is in good agreement with the structures **5** and **6**. The ^{1}H and ^{13}C NMR spectral patterns of **5** and **6** are very similar to each other and indicated that they are stereoisomer (diastereomer). To determine the

actual structures, NOE experiment of the main product was made and the result indicate that the bromine atom and the phenyl group are on *trans* position. But, there may be two conformational structures (**5** and **11**) in this position. The theoretical calculations (HyperChem 6.02 Semi-empirical (AM1), Molecular Mechanic (MM^+)) showed that conformer **5** is more stable than conformer **11** (Table-1). According to the results, it can be said that the bromine atom prefers the axial position because of the electronic repulsion between carbonyl oxygen and bromine atom. The other isomer should be in the structure of **6** due to preferring the equatorial position of phenyl group. Therefore, the results of the theorical calculations and NOE indicate that the *trans* isomer is preferably product **5** as shown in **Scheme-III**.

TABLE-1
THE CALCULATED TOTAL ENERGY (TE), BONDING ENERGY (BE), HEATS OF FORMATION (H_F) AND STRAIN ENERGY (SE) FOR CONFORMERS **5, 6, 10** AND **11**

Compd.	TE (kcal/mol)	BE (kcal/mol)	H_f (kcal/mol)	SE (kcal/mol)
5	-55102.07	-2837.71	-23.40	13.01
6	-55098.99	-2834.60	-20.29	14.17
10	-55100.79	-2836.40	-22.10	14.58
11	-55099.82	-2835.43	-21.13	15.98

2-Phenylcycloheptanone **12** reacted with PBr_5 in CCl_4 at room temperature to give a mixture of at least four ketones (^{13}C NMR shifts: 204.90, 204.72, 198.67, 197.64) (**Scheme-IV**). Furtheremore, ^{13}C NMR shifts of C-Br (at 76.25, 75.75, 52.73, 52.66, 52.61, 49.25 ppm) also indicate that there are four ketones. Two of them are α-bromiated ketones (**13**, **14**) and the others are α,α'-dibrominated ketones (**15, 16**). Accordig to the ^1H NMR spectrum of mixture, it is determined that the yield distrubition are 46:23 α-brominated ketones and 16:14 α,α'-dibrominated ketones. The two α-brominated ketones (**13** and **14**) seperated on a silica gel column, but the α,α'-dibrominated ketones (**15** and **16**) could not be isolated. We speculate that they convert to α,β-unsaturated ketones, which are decomposed.



12 **13** **14** **15** **16**

Scheme-IV

The structures of **13** and **14** were determined on the basis of spectra. The ^1H NMR spectra of **14** or **14** showed the proton neighbouring to bromine at 4.28 ppm as a doublet of doublet (J = 3.0 and 11.8 Hz) and of other isomer **13** or **14** at 3.73 ppm as a doublet of doublet (J = 4.2 and 11.2 Hz). In addition to the proton NMR, ^{13}C NMR spectra showed 11 lines for each isomer is in good agreement with the structures **13** and **14**. These results show that the **13** and **14** are the stereoisomer (diastereomer) with each other.

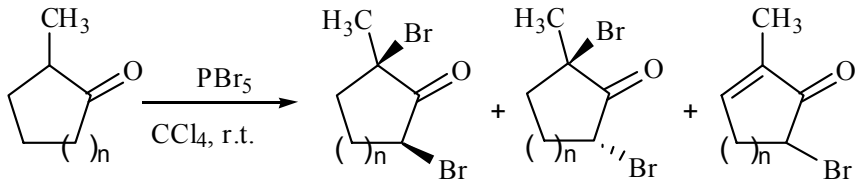
The reaction of 2-methylcycloheptanone **17c** with PBr_5 resulted in the formation of two α,α'-dibrominated ketones (**18c** and **19c**) (^{13}C NMR shifts: (C=O): at 208.54, 207.98 ppm; (CBr): at 68.41, 65.28, 52.07, 51.76 ppm) (**Scheme-V**). The mixture of products could not be separated chromatographically (on a silica gel column; moved together); its NMR spectra led to its assignment as a 60:40 mixture of two isomers.

The ^1H NMR spectra of **18c** and **19c** showed the proton neighbouring to bromine at δ = 5.12 ppm as a doublet of doublet (J = 2.95 and 11.83 Hz) and of other isomer **18c** or **19c** at 4.71 ppm as a doublet of doublet (J = 4.78 and 10.27 Hz). On the other hand, a 16 line ^{13}C NMR spectra of mixture are in good agreement with the structures of **18c** and **19c**. According to the results, it is concluded that the **18c** and **19c** are the stereoisomer (diastereomer) with each other.

From the reaction of 2-methylcyclohexanone **17b** with PBr_5, three products were obtained, which are separated on a silica gel column (**Scheme-V**). Two of these products are the α,α'-dibrominated ketones **18b** and **19b** and the other is α,β-unsaturated ketone **20b**. The latter product forms from the HBr elimination of **18b** and **19b**. The isolated yields of products **18b**, **19b** and **20b** are 47, 24 and 8.5 %, respectively.

The structures of **18b** and **19b** were explained by ^1H and ^{13}C NMR spectra. The ^1H NMR spectra of **18b** or **19b** showed the proton neighbouring to bromine at δ 5.56 ppm as a doublet of doublet (J = 6.1 and 12.9 Hz) and of other isomer **18b** or **19b** at 5.03 ppm as a doublet of doublet (J = 5.1 and 7.7 Hz). Furthermore, a 7 line ^{13}C NMR spectra for each isomers are in good agreement with the structures of **18b** and **19b**. According to the NMR results, it can be said that the **18b** and **19b** are the stereoisomer (diastereomer) with each other. It is concluded that the bromine atom perferred the axial position because of the electronic repulsion with carbonyl group.

2-Methylcyclopentanone (**17a**) reacts with PBr_5, to give a mixture of at least three ketones **18a**, **19a** and **20a** (^1H NMR shifts (CH_3) at 1.95, 2.04, 2.41 ppm) which rapidly decomposed at room temperature (**Scheme-V**). The species could not be purified and characterized. It was speculated that they are two α,α'-dibrominated 2-methylcyclopentanones **18a, 19a** and α,β-unsaturated ketone **20a** (^1H NMR shifts: at 7.2 ppm) or decomposition products therefrom.



17a-c **18a-c** **19a-c** **20a-c**

a: n = 1, b: n = 2, c: n = 3

Scheme-V

Consequently, we find that PBr_5 gives α-substitution with 2-substite ketones instead of the *geminal* addition.

According to the results obtained from the reaction of 2-phenylcyclohexanone **4** and 2-phenylcycloheptanone **12** with PBr_5, it is observed that the bromine atom has joined to the unsubstituted carbon as regioselective. In addition, it is indicated that the bromine atom has preferred to the axial position for the 2-phenylcyclohexanone (**4**). Furthermore, in case of 2-methylcycloketones, the regioselectivity was not observed in the addition of bromine atom, but bromine atom preferred to the axial position, too. The regioselectivity in the phenylketones depends on the steric effect of phenyl group.

It is known that 2-phenyl ketones are useful starting materials for the synthesis of biologically interesting compounds[17,18]. Hence, the compounds (**5, 6, 13** and **14**) may be employed in the synthesis of some biologically important compounds, because these compounds have either a phenyl group on the α-position or a bromine atom α'-position.

ACKNOWLEDGEMENTS

The authors are grateful to Department of Chemistry, Gaziosmanpasa University for financial support of this (Grant No. 2000/10 University Research Found). Thanks are also due to Dr. Cavit Kazaz, Atatürk University, Ataturk, Turkey for 200 MHz NMR spectrum.

REFERENCES

1. G. Wittig and P. Fritze, *Liebigs Ann. Chem.*, **82**, 711 (1968).
2. M. Balci and W.M. Jones, *J. Am. Chem. Soc.*, **102**, 7607 (1980).
3. Y. Sütbeyaz, M. Ceylan and H. Seçen, *J. Chem. Res. (S)*, 293 (1993).
4. Y. Sütbeyaz, M. Ceylan and H. Seçen, *J. Chem. Res. (M)*, 2189 (1993).
5. F. Tümer, Y. Taskesenligil, A. Dastan and M. Balci, *Aust. J. Chem.*, **49**, 599 (1996).
6. P.F. Hudrlik, A.K. Kulkarni, S. Jain and A.M. Hudrlik, *Tetrahedron*, **39**, 877 (1993).
7. G. Wittig and J. Meske-Schüller, *Liebigs Ann. Chem.*, **76**, 711 (1968).
8. A.T. Blomquist Jr., R.E. Burge and A.C. Sucsy, *J. Am. Chem. Soc.*, **74**, 3636 (1952).
9. A.T. Blomquist Jr., R.E. Burge and A.C. Sucsy, *J. Am. Chem. Soc.*, **74**, 3643 (1952).

10. J. Kagan, S.K. Arora, M. Bryzgis, S.N. Dhawan, K. Reid, S.P. Signh and L. Tow, *J. Org. Chem.*, **48**, 703 (1983).
11. P.F. Hudrlik and A.K. Kulkarni, *Tetrahedron*, **41**, 1179 (1985).
12. A.B. Brown, C.W. Chronister, D.M. Watkins, R.J. Mazzaccaro, S.R. Rajski, M.G. Fountain, S.E. McKay and T.L. Gibson, *Synth. Commun.*, **25**, 485 (1995).
13. H.-J. Ha, S.-K. Lee, Y.-J. Ha and J.-W. Park, *Synth. Commun.*, **24**, 2557 (1994).
14. L. Blanco, P. Amice and J.M. Conina, *Synthesis*, 194 (1976).
15. R.H. Reuss and A. Hassner, *J. Org. Chem.*, **39**, 1785 (1974).
16. M.W. Rathke and D. Vogaiazoglou, *J. Org. Chem.*, **52**, 3697 (1987).
17. B.C. Uff, G.G. Maghami, R.S. Budhram, C.L. Wilson and J.O. Apatu, *J. Heterocycl. Chem.*, **26**, 571 (1989).
18. D.S. Mortensen, A.L. Rodrigues, J. Sun, B.S. Katzenellenbogen and J.A. Katzenellenbogen, *Bioorg. Med. Chem. Lett.*, **1**, 1 (2001).

(*Received*: 28 February 2007; *Accepted*: 4 October 2007) AJC-5980