HETEROCYCLES, Vol. 31, No. 3, 1990

IMPROVING REGIOSELECTIVITY UNDER PHASE TRANSFER CONDITIONS: EFFECT OF CHEMICAL PARAMETERS AND KINETIC STUDY OF INDOLE N-ALKYLATION

Mohamed Bourak[a] and Roger Gallo*
ESIPSOI, UA 126 CNRS, Fac Sciences et Tech. St Jerome, 13013 Marseille, France
a ENS, BP 9172 Bd Victor Hugo, Mers Sultan Casablanca 03, Morocco

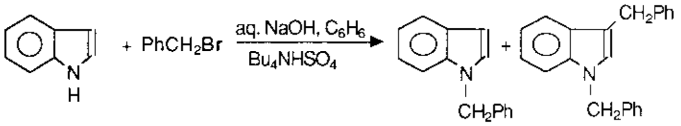
Abstract - The results obtained by changing the nature of catalyst, solvent, NaOH concentration, nature or ratio of reagents and reaction procedure are discussed for the alkylation of indole by benzyl halide under PTC conditions. Besides N-benzylindole other isomers are formed with the intermediate 3-benzylindole being detected at early reaction stage. Formation of benzyl alcohol(and ether) and of tertiary amine occurs in parallel. The relative rate constant with the leaving group chloride compared to bromide is 1/57, but the overall yield and selectivity in 1-alkylindole is increased. Rate constants and activation parameters are reported. Butyl and heptyl halides show similar behavior. The results are discussed in light of the general problem of change in nucleophilic ambident reactivity of heterocycles induced under phase transfer conditions.

Phase transfer catalysis is one of the most important recent methodological developments in organic synthesis.[1-9] Besides practical advantages and high versatility PTC gives important improvements in selectivity of organic reactions. This is specially true for azaaromatic heterocycles which behave as ambident molecules reacting at two or even more positions.[10] In this case PTC conditions are very favorable because the regioselectivity of the ambident anion is better controlled. However, several studies show that the direction of C vs heteroatom alkylation depends on several factors and, as concluded by Dehmlow in a recent review,[1] that : " a full quantitative understanding of the interactions of these factors has not yet been reached ". In the course of preparation of N-alkylindoles needed as synthetic intermediates we were faced to this problem; therefore we have studied the influence of chemical and physical parameters on alkylation of indole to better understand and hopefully predict the improvement in regioselectivity given by PTC in the alkylation of ambident heterocyclic nucleophiles.

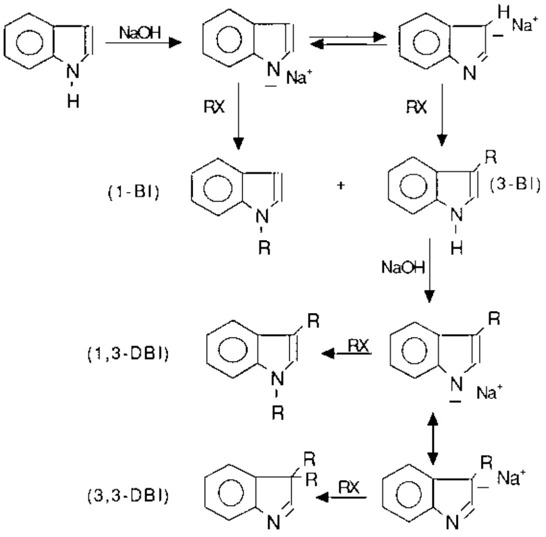
RESULTS AND DISCUSSION

The general method for preparation of N-alkylindoles has been the reaction of sodium salt generated from indole and sodium amide or sodium hydride.[11-15] This procedure was improved by the use of polar aprotic solvents (e.g. DMSO, HMPA, DMF, sulfolane).[16-20] More recently phase transfer with several types of catalysts[21-28] has been applied; in most cases the yields were higher and the presence of side products reduced. We have therefore used the standard conditions of liquid-liquid PTC similar to those described by Barco et al.[22] : in a biphasic solution containing NaOH 50%, $TBAHSO_4$, benzene and benzyl bromide, indole is added and the mixture is stirred magnetically during 3 hours at 33°C.

Under these conditions the yield in 1-benzylindole (1-BI) reaches a steady value of 79% ± 2%. The major side product was 1,3-dibenzylindole (1,3-DBI = 21%±2%); the other by-products occurred only as traces.



Scheme 1

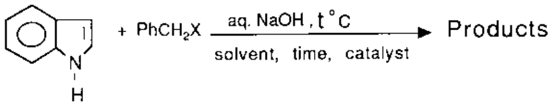


Scheme 2

In order to improve yield and selectivity in 1-BI, reaction parameters have been modified as reported in Table I. The yield in 1-BI ranges from 60 to 92% and, depending on conditions, not only 1,3-DBI but other products are formed in noticeable amounts; they are : 3-benzylindole, 3,3-dibenzylindolenine, benzyl alcohol, dibenzyl ether and tributylamine. A general scheme including reactions and equilibria involving the indole ring is given in Scheme 2.

Table I

Dependance of regioselectivity on reaction parameters



		Products Yields							
experiment	new parameter	indole[a]	1-BI[a]	3-BI[a]	1,3-DBI[a]	3,3-DBI[a]	Selectivity	$PhCH_2OH$	$(PhCH_2)_2O$
1	b	0[c]	79	0[c]	21	0[c]	3.7	0[c]	2
2	toluene[h]	0	74	0	26	0	2.8	0	2
3	33% NaOH	2	60	7	30	1	1.5	0	3
4	TBAB[d]	0	73	0	27	0	2.7	0	2
5	aliquat[e]	0	76	0	24	0	3.2	0	1
6	TEBA[f]	0	79	0	21	0	3.7	0	1
7	TBHDP[g]	0	75	0	25	0	3.0	0	2
8	$\frac{PhCH_2Br}{Indole} = 1$	10	69	11	10	0	3.2	0	1.5
9	t = 75°C	0	81	0	19	0	4.2	0	4
10	stirring = 60 rpm	0	79	0	21	0	3.7	0	2
11	C_6H_6 = 20 ml	0	82	0	18	0	4.5	0	3.5
12	aq. NaOH =10 ml	0	79	0	21	0	3.7	0	3.5
13	$PhCH_2Cl$	12	80	3	5	0	10.0	0	1
14	$\frac{PhCH_2Br}{Indole} = 2$	0	75	0	25	0	3.0	0	4
15	$PhCH_2Br$ dropwise	0	64	0	34	0	1.8	0	0.5
16	$PhCH_2Cl$ 18 h	0	91	0	9	0	10.1	0	0.5
17	$PhCH_2Cl$ 75°C	0	92	0	8	0	11.5	1	2.5

a % molar yield referred to indole
1-BI=1-benzylindole, 3-BI=3-benzylindole, 1,3-DBI=1,3-dibenzylindole, 3,3-DBI=3,3-dibenzylindolenine
b *experimental conditions given in* experimental section, general procedure
c The value 0 indicates trace amounts < 0.5% throughout the Table
d tetrabutylammonium bromide
e a technical grade of methyltrioctylphosphonium chloride
f triethylbenzylammonium chloride
g tributylhexadecylammonium bromide
h Toluene was tested in view of later development in organic synthesis because health regulation limits the use of benzene as solvent.

Scheme 2 is restricted to the formation of the ambident anion, depicted as its sodium salt, and to its chemical transformation. It does not include the exchange between the cations Na and quaternary onium and the associated transfer between phases which would make the picture to complex. The results of Table I show that some parameters are important on the change of selectivity (defined as the molar ratio S = 1-BI/ (1,3-DBI+3-BI+3,3-DBI); and that other parameters are not important, even if they are known to produce large variations on reaction rate constants.[29-35] The parameters inducing little or no change in selectivity ($2.7 < S > 4.5$) are :

the nature of the quaternary onium catalyst (exps. 4-7); $TBAHSO_4$ (exp.1) and TEBA (exp. 6) giving the best result.

the temperature (exps. 1 and 9; 16 and 17); however in this case more dibenzyl ether is detected,

the stirring rate (exp. 10); indicates that the reaction is on chemical and not physical control,

the relative concentration of reagents $PhCH_2Br$/indole from an excess (exp. 14) to an equimolarity (exp. 8),

the volume and nature of solvent (exps. 2 and 11); the two aromatic solvents being very similar.

the volume of aqueous NaOH (exp. 12).

These results are in agreement with a previous study of 2- and 4-hydroxypyridine alkylation where alterations in reaction conditions (catalyst, solvent, temperature) did not profoundly affect the reaction selectivity.[36] On the other hand, parameters giving changes in selectivity are :

the concentration (not the volume) of aqueous NaOH (exp. 3),

the experimental procedure(exp. 15); introducing dropwise the benzyl bromide affords a poor selectivity and as expected reduces the dibenzyl ether because the instant concentration of bromide in the reaction medium, and its hydrolysis, is smaller.

The nature of leaving group (exp. 13); when benzyl chloride was used under conditions of experiment 1 the increase in selectivity is important (S= 10) but 18% of indole was not reacted. When working at longer reaction time (exp. 16) or higher temperature (exp. 17) indole reacts completely and the same selectivity is observed (S= 10.1, 11.5) . Most of the observations made are in agreement with the theory of PTC, and with the multiparameter dependance of ambident anion selectivity[37-39] summarized by Le Noble : "the freer the anion the greater the tendency for alkylation at the most electronegative center.[40] A hard leaving group (chlorine) increases the N/C alkylation ratio in agreement with previous observations made with the O/C alkylation ratio of enolates.[41-46] A less concentrated NaOH solution implies the transfer of a limited number of water molecules in the organic phase, with a consequent specific solvation of the anion,[47-50] since water molecules complex preferably to the harder nitrogen then more C-alkylation is observed. However the apparent random occurrence of 3-BI, of dibenzyl ether and of tributylamine needed a closer examination. A kinetic study was undertaken to verify the mechanistic scheme proposed and to obtain quantitative informations on the relation between reaction rates and selectivity.

The evolution of products concentration is depicted in Figure 1, with benzyl bromide as alkylating agent, and on Figure 2 with benzyl chloride.

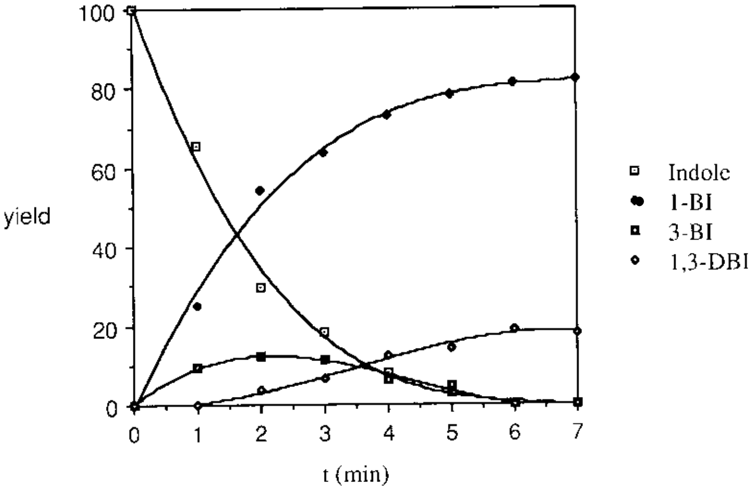


Figure 1: % of products time dependance in the reaction between indole and benzyl bromide

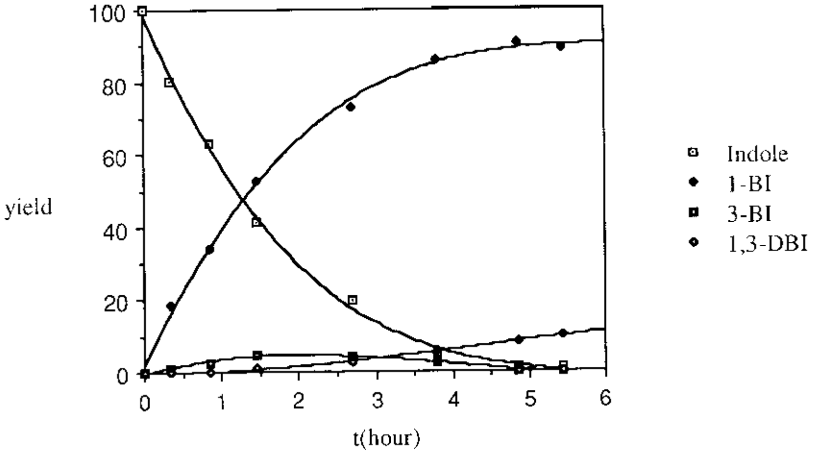


Figure 2: % of products time dependence in the reaction between indole and benzyl chloride

There are striking features:

both graphs are typical of the competitive parallel and consecutive process postulated. With benzyl bromide reaction is complete within 6 minutes (compared to a 18 h reaction time reported before).[22] 3-BI occurs at early reaction times due to lower leaving group ability or to smaller base concentration which reduce reaction rate; 3-BI occurs also with equimolar amounts of reagents since part of $PhCH_2Br$ is hydrolysed to benzyl alcohol and converted to dibenzyl ether;[51] consequently 3-BI is not further benzylated.

Several attempted estimations of each rate constant involved in the competititive process failed because the kinetic equations are complicated by the dependance of reagents concentration on exchange coefficients between phases. However, a calculation was made on the disappearence of indole under pseudounimolecular conditions observed in previous studies.[29-35] A kinetic plot is depicted in Figure 3; the results are summarized in Tables II and III.

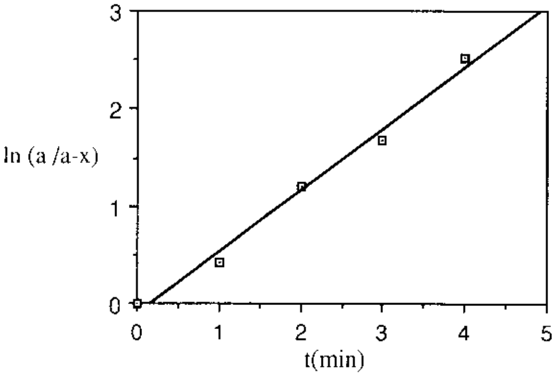


Figure 3: kinetic plot for the reaction : indole + $PhCH_2Br$ (exp.18)

Table II

Pseudounimolecular rate constants for the reaction : indole + $PhCH_2X$

exp	$PhCH_2X$	solvent	t°C	$k.10^4$ sec^{-1} [a]
18	$PhCH_2Br$	C_6H_6	33.0	98.
19	$PhCH_2Cl$	C_6H_6	33.0	1.7
20	$PhCH_2Cl$	toluene	33.5	1.0

[a] The rate constants are mean values of repeated experiments calculated with a least square regression analysis using the data up to 90% reaction complexion.

Table III

Dependance of pseudounimolecular rate constants on catalyst concentration and temperature for indole + $PhCH_2Cl$

exp	solvent	t°C	indole/catalyst[a]	$k.10^4$ sec^{-1}
21	toluene	33.5	20	1.02
22	toluene	33.5	17	1.23
23	toluene	33.5	14	1.31
24	toluene	39.5	20	1.59
25	toluene	57.5	20	8.10

a molar ratio

The leaving group ability of bromide compared to chloride is 57; it is in the range observed recently by Landini et al. (40-179) for nucleophilic substitutions promoted by quaternary onium salts.[55] The less reactive chloride is more selective as in many cases according to the controversial reactivity-selectivity principle (R.S.P.). The linear dependance of the pseudounimolecular rate constant with catalyst concentration in table III has been observed in PTC when no important change of catalyst partitioning between the two phases occurs during the course of the reaction.

The activation parameters derived from (exp. 23-25) are : E = 17.6 Kcal/mol (73.8 Kjoule/mol); LogA= 19.71; $\Delta H^{\neq}$= 17.0 Kcal/mol (71.1 Kjoule/mol); $\Delta S^{\neq}$ = -21.4 e.u. They are in agreement with bimolecular substitution reactions. The value of $\Delta H^{\neq}$= 17.0, larger than $\Delta H^{\neq}$= 13.9 observed by Dubois et al. for the PT ether synthesis, seems inconsistent with the increase in dibenzyl ether at high temperature (Table I). In fact the experiments of Table I were conducted changing only one parameter; and a higher temperature, with the same reaction time, corresponds to a steady yield of alkylindole but to an increased hydrolysis and etherification of the excess benzyl halide. There is a right balance to find between ratio of reagents and temperature to achieve a complete alkylation and prevent a decomposition of the excess halide. The only not reproducible value (which never exceeded 1%) was the *tributylamine concentration. It changed for the same reaction* when gpc analyses were conducted at different reaction times after the organic layer was withdrawn from the reaction medium. This proved to be an artefact which disappeared during the kinetic study with appropriate quenching : Tributylamine has been alkylated by excess benzyl halide even out of the presence of a basic solution whereas all the other compounds were stable. On the other hand the origin of tributylamine is clearly the result of the decomposion of the quaternary ammonium catalyst as observed earlier : it was shown that a tertiary amine is displaced as a leaving group in substitution or Hofmann type eliminations under PTC conditions. The results of Table IV show that butyl and heptyl bromide, of lower reactivity than benzyl bromide, give selectivities comparable to those observed with benzyl chloride. Here again change in temperature and catalyst ratio have little effect on selectivity.

Table IV

% of alkylation products for reaction

indole + RX $\longrightarrow$ products

exp	RX	ratio indole/ catalyst	t°C	1-RI	1,3-DRI
26[a]	nC_4H_9Br	20	33.0	95	5
27	nC_4H_9Br	14	33.0	95	5
28	nC_4H_9Br	20	64	93	7
29	$nC_7H_{15}Br$	20	33.0	88	12
30	$nC_7H_{15}Br$	20	64.0	88	12

In summary the improvement of selectivity in PTC alkylation of indole is a complex multiparameter problem. Chemical and physical parameters modify the regioselectivity of alkylation by changing the nature of the ion pair formed with the quaternary ammonium salt, but also produce side reactions. PTC has advantages and limitations. The advantages are that the procedure is simple and economical, and the results in regioselectivity superior to those observed under conventional procedures or with polar aprotic solvents. The limitations come from partial hydrolysis of the alkylating agent and decomposition of the catalyst; a correct balance needs to be found.

EXPERIMENTAL

Materials and method

Nuclear magnetic resonance spectra were obtained on a EM 360 Varian 60 MHz spectrometer, with TMS as an internal standard, for ^1H; and on a AM 250 Brucker 250 MHz spectrometer for ^{13}C. Gpc analyses were performed on a INTERSMAT IGC 16 chromatograph equiped with a 5 ft x 0.125 inch column packed with 10% SE 30 on chromosorb PAW 80/100. Coupled gpc-ms spectra were obtained on a Ribermag R-1010 C apparatus. Melting points were determined on a Büchi apparatus and are uncorrected. Elemental analysis are in satisfactory agreement with calculated values. Rate constants and activation parameters were calculated on an Apple II microcomputer.Indole, benzyl bromide, benzyl chloride, butyl bromide and heptyl bromide are commercial products (purum grade); they were distilled prior to use. Benzene, toluene and quaternary ammonium catalysts were obtained commercially and used without purification.

General procedure for N-alkylation of indole.

The following conditions are used except when one or several parameters are changed as indicated in Tables: a solution of 10 ml of NaOH (50% by weight), 10 ml of benzene, 15 mmol of alkylating agent, 10 mmol of indole, 0.5 mmol of $TBAHSO_4$ is stirred magnetically during 3 h at 33.0 °C, 10 ml of water is added, the organic layer is collected, the aqueous layer is extracted with 10 ml of benzene. The combined organic solutions are washed with a 10% HCl solution, water dried over $MgSO_4$. concentrated at reduced pressure and analyzed by gpc.

Kinetic measurements

An aqueous solution of 40 ml of NaOH (50% by weight), 40 ml of indole and 2-2.8 mmol of catalyst is stirred at constant temperature (see Table II) during 15 min. At zero time 60 mmol of $PhCH_2X$ are added. Samples are withdrawn periodically, quenched and analysed by gpc. The first order rate constants and the parameters from Arrhenius and Eyring equations were evaluated using a least-square regression analysis program.

N-Benzylindole

The general procedure afforded a liquid. Distillation (bp 140-142°C, 5 mm) gave white crystals (mp 44-45°C) turning pink on contact with air and light.^{1}HNmr ($CDCl_3$) δ 6.70-7.80 (10H, m), 6.50 (1H, d, J= 3.0 Hz), 5.20 (2H, s).^{13}CNmr ($CDCl_3$) 137.58, 136.43, 128.72, 128.15, 127.74, 127.56, 126.81, 121.7, 121.0, 119.55, 109.66,101.75, 50.04, Ms; m/z (%) 207(50), 91(100), 65(12).

N-Butylindole

Distillation of the product obtained by the general procedure affords a colorless liquid (bp 144-145°C 14 mm). ^{1}HNmr($CDCl_3$) δ 6.80-7.80(5H, m), 6.45(1H, d, J=4 Hz), 3.98(2H, t, J=7.4 Hz), 1.95- 0.65(7H, m). ^{13}CNmr($CDCl_3$) 136.05, 128.72, 127.54, 121.20, 120.85, 119.09, 100.81, 45.67, 32.12, 19.65, 13.52. Ms, m/z(%) 173(82), 131(73), 130(100), 117(27), 103(31), 77(36), 63(19), 51(24), 39(45).

N-Heptylindole

Distillation of the product obtained by the general procedure affords a pale yellow liquid (bp 140-142°C 3 mm). ^{1}HNmr ($CDCl_3$) δ 6.80-7.70(5H, m), 6.45(1H, d, J=4 Hz), 3.97(2H, t, J=7.2 Hz), 2.10-0.60(13H, m). ^{13}CNmr($CDCl_3$) 136.02, 128.67, 127.62, 121.26, 120.91, 119.14, 100.87, 46.29, 31.72, 30.23,28.91, 26.94, 22.58, 14.02. Ms, m/z (%) 215(11), 130(100), 117(12), 103(6), 63(4), 55(7), 41(16).

REFERENCES AND NOTES.

1 E. V. Dehmlow and S. S. Dehmlow, "Phase Transfer Catalysis", 2nd Ed. Verlag Chemie, Weinheim, 1983.

2 C. M. Starks and C. Liotta, " Phase Transfer Catalysis", Academic Press, New York, 1978.

3 W. P. Weber and G. W. Gokel, "Phase Transfer Catalysis in Organic Synthesis", Springer-Verlag, Berlin, 1977.

4 W. E. Keller, " Compendium of Phase Transfer Rections", Fluka AG, Buchs, Switzerland, 1986.

5 M. Makosza, *Surv. Prog. Chem.*, 1980, **9**, 1.

6 G. W. Gokel and W.P. Weber, *J. Chem. Ed.*, 1978, **55**, 350.

7 J. M. Lehn, *Acc. Chem. Res.*, 1978, **11**, 49.

8 E. Weber and F. Vogtle, *Top. Current. Chem.*, 1981, **98**, 1.

9 F. Montanari, D. Landini, and F. Rolla, *Top. Current. Chem.*, 1982, **101**, 147.

10 R. Gallo, H. Dou, and P. Hassanaly, *Bull. Soc. Chim. Belg.*, 1981, **90**, 849.

11 K. T. Potts and J.E. Saxton, *J. Chem. Soc.*, 1954, 2641.

12 W. Julia and P. Manoury, *Bull. Soc. Chem. France*, 1964, 1946.

13 S. Yamada, *Chem. Pharm. Bull.*, 1965, **13**, 88.

14 A. H. Jackson and A. E. Smith, *Tetrahedron*, 1965, **21**, 989.

15 B. Cardillo, G. Casnati, A. Pochini, and A. Ricca, *Tetrahedron*, 1967, **23**, 3771.

16 H. Normant and T. Cuvigny, *Bull. Soc. Chim. France*, 1965, 1866.

17 G. M. Rubottom and J. C. Chabala, *Synthesis*, 1972, 566.

18 H. Heaney and S. V. Levy, *J. Chem. Soc., Perkin Trans. I*, 1973, 499.

19 R. Garner, P. J. Albisser, M. A. Penswick, and M. J. Whitehead, *Chem. Ind.*, 1974, 110.

20 Y. Kikugawa and Y. Miyake, *Synthesis*, 1981, 461.

21 A. Jonczyk and M. Makosza, *Roczniki Chem.*, 1975, **49**, 1203.

22 A. Barco, S. Beneti, and G. P. Pollini, *Synthesis*, 1976, 124.

23 V. Bocchi, G. Casnati, A. Dossena, and F. Villani, *Synthesis*, 1976, 414.

24 E. Santaniello, C. Farachi, and F. Ponti, *Synthesis*, 1979, 617.

25 W. C. Guida and D. J. Mathre, *J. Org. Chem.*, 1980, **45**, 3172.

26 M. Sukata and S. Kazuaki, *Bull. Chem. Soc. Jap.*, 1983, **56**, 280.

27 J. Barry, G. Bram, G. Decodts, A. Loupy, P. Pigeon, and J. Sansoulet, *Tetrahedron*, 1983, **39** 2669.

28 R. S. Davidson, A. M. Patel, and A. Safdar, *J. Chem. Res(S)*, 1984, 88.

29 A. W. Heriott and D. Picker, *J. Am. Chem. Soc.*, 1975, **97**, 2345.

30 C. M. Starks, *J. Am. Chem. Soc.*, 1971, **93**, 195.

31 C. M. Starks and R. M. Owens, *J. Am. Chem. Soc.*, 1973, **95** 3613.

32 H. H. Freedman and R. A. Dubois, *Tetrahedron Lett.*, 1975, 3521.

33 D. Landini, A. M. Maia, F. Montanari, and J. M. Pirisi, *J. Chem. Soc., Chem. Comm.*, 1975, 950.

34 R. Solaro, S. D' Antone, and E. Chiellini, *J. Org. Chem.*, 1980, **45**, 4179.

35 J. E. Gordon and R. E. Kutina, *J. Am. Chem. Soc.*, 1979, **99**, 3903.

36 H. Dou, P. Hassanaly, and J. Metzger, *J. Heterocycl Chem.*, 1977, **14**, 321.

37 E. D'Incan and P. Viout, *Tetrahedron*, 1975, **31**, 159.

38 C. Cambillau, P. Sarthou, and G. Bram., *Tetrahedron Lett.*, 1976, 281.

39 F. Guibi and G. Bram, *Bull. Soc. Chim. France*, 1975, 933.

40 W. J. Le Noble, "Highlights of Organic Chemistry", Marcel Dekker, New York, 1974.

41 E. M. Arnett and W. M. De Palma, *J. Am. Chem. Soc.*, 1976, **98**, 2447.

42 E. A. Noe and M. Raban, *J. Am. Chem. Soc.*, 1974, **96**, 6184.

43 M. Halpern, Y. Sasson, I. Willner, and M. Rabinovitz, *Tetrahedron Lett.*, 1981, **23**, 1719.

44 A. Brandstrom and U. Junggren, *Acta Chem. Scand.*, 1971, **25**, 1469.

45 A. Mc Killop, J. C Fiaud, and R. P. Hug, *Tetrahedron*, 1974, **30** 1379.

46 A. P. Bashall and F. J. Collins, *Tetrahedron Lett.*, 1975, 3484.

47 D. Landini, A. Mario, and G. Podda, *J. Org. Chem.*, 1982, **47**, 2264.

48 J. P. Antoine, I. De Aguirre, I. Jansens, and F. Thyrion, *Bull. Soc. Chim. France*, 1980, 207.

49 D. Landini, A. Maia, and F. Montanari, *J. Am. Chem. Soc.*, 1978, **100**, 2796.

50 D. Landini, A. Maia, F. Montanari, and P. Tundo, *J. Am. Chem. Soc.*, 1979, **101**, 2526.

51 Note that one could take advantage of this hydrolysis side reaction, which was observed earlier by Heriott and Picker[52] and by Freedman and Dubois,[32] to prepare directly

symetrical ethers from halides under PT conditions. In fact this would be of practical the case of $PhCH_2Cl$ prepared by industrial photochemical chloration of toluene.[53]

52 A. W. Heriott and D. Picker, *Tetrahedron Lett.*, 1972, 4521.

53 When this work was in the course a patent was issued describing the PT synthesis of benzyl ether from benzyl halide.[54]

54 A. T. Babayan, G. O. Torosyan, and S. L. Paravyan, *Chem. Abstr.*, 1984, 100, 22402t, Okrytia, Isobret., Prom. Obraztsy, *Tovarnye Znaki*, 1983, **30**, 71.

55 D. Landini, A. Maïa, F. Montanari, and F. Rolla, *J. Org. Chem.*, 1983, **48**, 3774

Received, 17th November, 1988