Catalytic Alkylation, Sulphonation, and Heteroarylation of Some Bicyclic Pyrazolines in Solid-Liquid Two Phase Systems

Ahmed Kamal El-Shafei,* Ahmed Mahmoud El-Sayed, and Ali Ali Khalaf†
Chemistry Department, Faculty of Sciences, Sohag University, Sohag, Egypt
†*Chemistry Department, Faculty of Sciences, Assiut University Assiut, Egypt*

(Received March 29, 1982)

The reaction of some bicyclic pyrazolines with alkyl halides, aryl sulphonyl chlorides as well as with some N–H and S–H containing heterocycles is affected in solid-liquid two phase systems using a catalyst. The catalytic cycle is described, the purity of the obtained products is checked using TLC and their structure is confirmed by a combination of chemical and spectroscopic methods.

It has been recognized recently[1] that numerous N–H acidic compounds can be conveniently alkylated in the presence of concentrated aqueous sodium hydroxide or potassium hydroxide solutions and quaternary ammonium salts as catalysts. The catalytic method has been used for alkylation of aziridine,[2] phenothiazine,[3] pyrrole,[4] indole,[4–7] and its derivatives,[5] diphenylamine,[4] carbazole,[4] some amides,[8] and phenylhydrazones of aldehydes and ketones.[9] These reactions take place in liquid-liquid two phase system in which both phases, aqueous sodium hydroxide and organic reactants (neat or in nonpolar solvent) are mutually immiscible. This catalytc two phase (CTP) system offers numerous advantages over other bases such as NaH, $NaNH_2$, and *t*-BuOK *inter alia* elimination of hazardous and expensive reactants, anhydrous organic solvents, *etc.*

Despite many advantages, the CTP system has some limitations, one of them being the hydrolytic activity of concentrated aqueous alkali. However, it has been reported that many reactions with C–H acidic compounds can be efficiently carried out using anhydrous sodium or potassium carbonate as bases.[9–11] In these cases the reactions proceed in liquid-solid two phase systems, organic reactants neat (if liquids) or in aprotic solvents form the organic phase in which solid sodium or potassium carbonate is suspended. In these systems reactions are catalyzed by tetraalkylammonium salts or crown ethers. The catalysts are unable to transfer carbonate anions (CO_3^{2-}) into the organic phase,[12] thus solid-liquid phase-transfer phenomena are probably not involved here. It is more plausible that the first step, namely proton abstraction, takes place on the surface of the solid carbonate (see Fig. 1). The anions formed then migrate into the organic phase as ion pairs with the catalyst cation. Since several reports indicated the pharmacological importance[13–16] of some bicyclic pyrazolines, we report here the synthesis of some new derivatives of 7-benzylidene-3,3a,4,5,6,7-hexahydro-3-phenyl-2*H*-indazole (**1**) using solid-liquid two phase transfer system. This method offers a convenient synthetic means due to the comparative stability of such compounds.[17] Compound **1** was obtained by refluxing 2,6-dibenzylidenecyclohexanone with hydrazine hydrate in methanol.

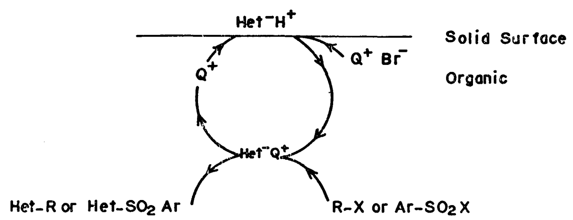
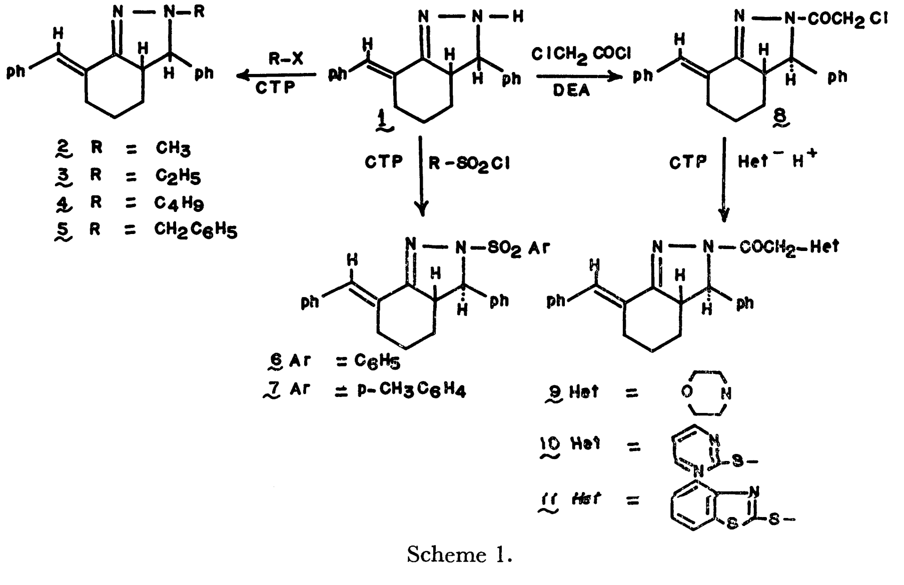


Fig. 1. Catalytic two phase solid-liquid cycle.

The alkylation and sulphonation of **1** in CTP system



Scheme 1.

TABLE 1. PREPARATION OF ALKYLATED, SULPHONATED, AND HETEROARYLATED BICYCLIC PYRAZOLINES USING CTP SYSTEM

Product	Reaction conditions Temperature °C	Reaction conditions Time h	Yield %	Mp θ_m/°C	Mol formula (Mol wt.)	Calcd (Found) (%) C	Calcd (Found) (%) H	Calcd (Found) (%) N	TLC R_f
1	See experimental		82	84—86	$C_{20}H_{20}N_2$ (288)	83.33 (83.21)	6.94 (7.06)	9.72 (9.80)	0.6[a]
2	33	2.5	65	233—235	$C_{21}H_{22}N_2$ (302)	83.44 (83.37)	7.28 (7.31)	9.27 (9.29)	0.2
3	33	2.5	74	164—165	$C_{22}H_{24}N_2$ (316)	83.54 (83.59)	7.59 (7.62)	8.86 (8.78)	0.1
4	33	4	61	103—105	$C_{24}H_{28}N_2$ (344)	83.72 (83.83)	8.13 (8.09)	8.13 (8.19)	0.3
5	33	3	82	137—138	$C_{27}H_{26}N_2$ (378)	85.71 (85.68)	6.87 (6.85)	7.40 (7.29)	0.7
6	33	2	87	210	$C_{26}H_{24}N_2SO_2$ (428)	72.89 (72.96)	5.60 (5.64)	6.54 (6.48)	0.7
7	33	2	82	226—227	$C_{27}H_{26}N_2SO_2$ (442)	73.30 (73.41)	5.88 (5.92)	6.33 (6.42)	0.7
8	See experimental		43	151—153	$C_{22}H_{21}N_2OCl$ (364.5)	72.42 (72.60)	5.76 (5.69)	7.68 (7.56)	0.2
9	40	2	75	90—92	$C_{26}H_{29}N_3O_2$ (415)	75.18 (75.09)	6.98 (7.06)	10.12 (10.04)	0.7
10	33	4	66	218	$C_{26}H_{24}N_4SO$ (440)	70.90 (70.99)	5.45 (5.39)	12.72 (12.86)	0.3
11	33	4	58	165	$C_{29}H_{25}N_3S_2O$ (495)	70.30 (70.22)	5.05 (5.12)	8.48 (8.31)	0.6

a) Eluted in CH_2Cl_2.

TABLE 2. ^{1}H-NMR SPECTRAL DATA OF THE PREPARED BICYCLIC PYRAZOLINE DERIVATIVES USING CTP SYSTEM

Compound	NMR δ
1	7.50—7.05 (m, 10H, Ar), 6.9 (m, 1H, =CH), 6.50 (s, 1H, NH), 4.35 (t, 1H, N-CH), 3.0—0.90 (m, 7H, aliph.) (DMSO-d_6)
2	7.68—7.18 (m, 10H, Ar), 7.10 (m, 1H, =CH), 4.85 (t, 1H, N-CH), 3.55 (s, 3H, CH_3), 3.30—0.9 (m, 7H, aliph.) (CF_3COOD)
3	7.65—7.00 (m, 11H, Ar+=CH), 5.0 (t, 1H, N-CH), 3.30—0.9 (m, 12H, aliph.) (CF_3COOD)
4	7.60—6.80 (m, 11H, Ar+=CH), 4.80 (t, 1H, N-CH), 3.30—0.60 (m, 16H, aliph.) (CF_3COOD)
5	7.67—6.68 (m, 16H, Ar+=CH), 4.55 (t,, 1H, N-CH), 3.80 (s, 2H, CH_2), 3.30—0.95 (m 7H, aliph.) (CF_3COOD)
6	8.10—7.00 (m, 16H, Ar+=CH), 5.60 (t, 1H, N-CH), 3.35 (m, 7H, aliph.) (pyridine-d_5)
7	8.15—7.05 (m, 15H, Ar+=CH), 4.25 (t, 1H, N-CH), 3.15—0.80 (m, 10H, aliph.+*p*-CH_3) (pyridine-d_5)
8	7.55—7.10 (m, 10H, Ar), 7.00 (s, 1H, =CH), 5.00 (t,1H, N-CH), 3.48 (t, 2H, CH_2), 3.00—1.00 (m, 7H, aliph.) ($CDCl_3$)
9	7.40—7.00 (m, 11H, Ar+=CH), 4.80 (t, 1H, N-CH), 3.82—3.15 (m, 8H, aliph.), 3.10—0.75 (m, 9H, aliph.+CH_2) ($CDCl_3$)
10	8.92—8.68 (m, 3H, pyrimidine), 7.68—6.70 (m, 11H, Ar+=CH), 4.83 (t, 1H, N-CH), 3.45—0.75 (m, 9H, aliph. +CH_2) (CF_3COOD)
11	7.95—6.85 (m, 15H, Ar+=CH+2-benzothiazolyl-), 4.80 (t, 1H, N-CH), 3.35—0.80 (m, 9H, aliph.+CH_2) (CF_3COOD)

was affected in potassium carbonate-acetone using tetrabutylammonium bromide (TBAB) as a catalyst. Time of the reaction at the appropriate temperature was summarized in Table 1. The reactions were monitored by TLC and the identity of the obtained products was based on both microanalytical and NMR data. The starting bicyclic pyrazoline **1** was chloroacetylated by stirring an equimolar mixture of **1** and chloroacetyl chloride in benzene at 18 °C for 1 h. The *N*-chloroacetylpyrazoline derivative **8** was effectively used as an alkylating agent to some N–H and S–H containing heterocycles, namely, morpholine, 2-mercaptopyrimidine, and 2-mercaptobenzothiazole. The reactions were performed in CTP system (K_2CO_3/acetone/TBAB) where the corresponding dehydrochlorinated products **9**, **10**, and **11**, respectively were obtained in fair yields. Figure 1 illustrate the catalytic cycle where Het$^-$ corresponds to cations derived from N–H or S–H containing heterocycles used in CTP reactions, Q$^+$ to tetrabutylammonium cation and R$^+$ to alkyl or *N*-acetylpyrazolinyl cations.

Experimental

Melting points are uncorrected and were determined using a Kopfler bank. ^{1}H-NMR spectra were obtained on a Varian EM 360 A or NV 14 spectrometer at 60 MHz or at 100 MHz using TMS as an internal standard, chemical shifts are expressed in ppm. Qualitative thin layer analyses were carried out using nanoplates (10 cm × 10 cm, HPTLC, 5 μm silica) with nitromethane as eluent.

Catalytic Two Phase Alkylation and Sulphonation of N–H Containing Compound 1. General Procedure: To a mixture of compound **1** (0.05 mol) and potassium carbonate (0.05 mol) in acetone (70 ml) an equimolar amount of alkyl halide or aryl sulphonyl chloride (0.05 mol) was added. The mixture was treated with a catalytic amount of tetrabutylammonium bromide (TBAB) (0.001 mol), and vigorously stirred at the appropriate temperature (see Table 1) over periods of time ranging between 2—6 h. After completion of the reaction (TLC) the mixture was filtered off, dried ($MgSO_4$), evaporated *in vacuo* and the residual solid was crystallized from the appropriate solvent.

Synthesis of N-*Chloroacetyl Bicyclic Pyrazoline Derivative 8.* To a solution of 0.01 mol of compound **1**, 0.015 mol of *N*,*N*-diethylaniline in 50 ml of benzene, 0.012 mol of chloroacetyl chloride in few ml of benzene was gradually added under efficient stirring, the reaction mixture was stirred at 18 °C for 1 h and was then evaporated *in vacuo*. The obtained solid was washed with water followed by petroleum ether 60—80 °C, dried and crystallized from dioxane.

Reaction of N-*Chloroacetylpyrazoline Derivative 8 with N–H and S–H Containing Heterocycles Using CTP System. General Procedure*: Compound **8** (0.05 mol) along with 0.05 mol of potassium carbonate in acetone (70 ml) was treated with 0.05 mol of morpholine, 2-mercaptopyrimidine, or 2-mercaptobenzothiazole, in presence of a catalytic amount of TBAB (0.001 mol). The reaction mixture was vigorously stirred at the appropriate temperature for a certain time (see Table 1). After filtration the mixture was dried ($MgSO_4$), evaporated *in vacuo* to give the desired products **9**, **10**, or **11**.

References

1) R. Gallo, H. J-M Dou, and P. Hassanaly, *Bull. Soc. Chim. Belg.* **90**, 849 (1981).

2) M. Maurette, A. Lopez, R. Martino, and A. Lattes, *C. R. Acad. Sci., Ser. C*, **282**, 599 (1976).

3) H. Wunderlich, W. Lugenheim, A. Stark, and G. Detrekoi, *Pharmazie*, **21**, 57 (1966).

4) A. Jonczyk and M. Makosza, *Rocz. Chem.*, **49**, 1203 (1975).

5) N. N. Suvorov, Y. J. Smushkevich, V. S. Velezheva, V. S. Rozhkov, and S. V. Simakov, *Khim. Geterotsikl. Soedin.*, **1976**, 191.

6) A. Barco, S. Benetti, G. P. Pollini, and P. G. Baraldi, *Synthesis*, **1976**, 124.

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

8) R. Brehme, *Synthesis*, **1976**, 113.

9) A. Jonczyk, J. Wlostowska, and M. Makosza, *Synthesis*, **1976**, 795.

10) D. A. White, *Synth. Commun.*, **7**, 559 (1977) and references cited therein.

11) R. M. Boden, *Synthesis*, **1975**, 784.

12) M. Fedorynski, K. Wojciechowski, Z. Matacz, and M. Makosza, *J. Org. Chem.*, **43**, 4682 (1978).

13) J. Krapcho and C. Turk (Squibb, E. R. and Sons. Inc.) U. S. Patent 3 957 762 (cl. 260—240D; Co 7D 231/56) 18 May 1976, Appl. 469, 171, 13 May 1974; *Chem. Abstr.*, **85**, 63066b (1976).

14) J. Krapcho and C. Turk, Ger. Offen 2 521 299 (cl O and D), 27 Nov. 1975, U. S. Appl. 469, 171, 13 May 1974; *Chem. Abstr.*, **84**, 59455q (1976).

15) J. Krapcho and C. Turk, (Squibb, E. R. and Sons Inc.) U. S. Patent 4 004 007 (cl. 424—246); (07D 487/OZ), 18 Jan. 1977, Appl. 603, 222, 8 August 1975; *Chem. Abstr.*, **86**, 171443b (1977).

16) J. Krapcho and C. Turk, *J. Med. Chem.*, **22**, 207 (1979).

17) Gy. Oszbach and D. Szabo, *Acta Chim. Acad. Sci. Hung.*, **86**, 449 (1975).