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2-DIALKYLAMINOPYRIDINIUM SALTS AS NEW TYPE OF CATALYSTS IN TWO-PHASE ALKYLATION REACTION

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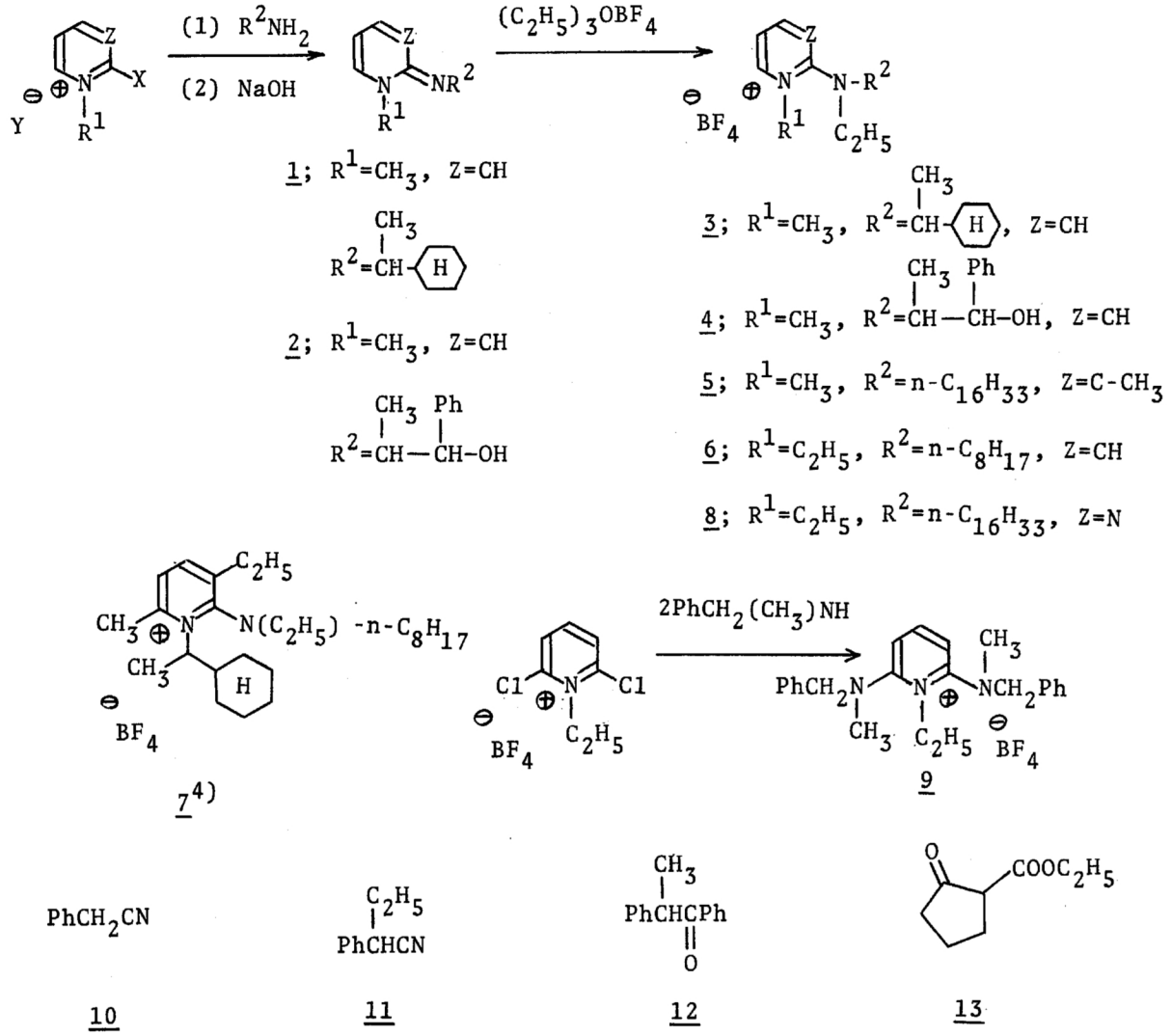
2-Dialkylaminopyridinium salts, derived from 2-halopyridinium salts and primary or secondary amines, were effectively employed as catalysts in the two-phase alkylation reaction of active methylene compounds with alkyl halides to afford the corresponding alkylated products in good yields.

Since onium compounds were efficiently used as catalysts in the two-phase reaction, a number of studies[1,2] in this field have led this reaction to a useful technique in organic synthesis. In the previous communications,[3] we reported the synthetic utilities of 2-halopyridinium salts and, in connection with these observations, we now wish to report that 2-dialkylaminopyridinium salts (3 - 9), readily derived from various 2-halopyridinium salts and primary or secondary amines, catalyze the two-phase alkylation reaction of active methylene compounds with alkyl halides to afford the corresponding alkylated products in good yields.

The following procedure is representative for the preparation of 2-dialkylaminopyridinium salts (Scheme). A solution of hexadecylamine (1.20 g, 5.0 mmol) and triethylamine (505 mg, 5.0 mmol) in dichloromethane (25 ml) was slowly added at room temperature to a stirred solution of 2-chloro-1,3-dimethylpyridinium methylsulfate (1.27 g, 5.0 mmol) in dichloromethane (5 ml), and then the resulting mixture was refluxed for 1 hr. After evaporation, the residue was treated with 10% aqueous sodium hydroxide (20 ml) at room temperature for 2 hr and the mixture was extracted with dichloromethane (3 x 20 ml). The organic layers were combined, washed with water, dried (Na_2SO_4), and concentrated to give almost pure 2-hexadecylimino-1,3-dimethyl-1,2-dihydropyridine (1.71 g, 4.9 mmol, 98%). The iminopyridine reacted with triethyloxonium tetrafluoroborate (950 mg, 5.0 mmol) in dichloroethane (5 ml) to give

Scheme



2-ethylhexadecylamino-1,3-dimethylpyridinium tetrafluoroborate (5) (2.08 g, 4.5 mmol, 90%). Similarly, 2-dialkylaminopyridinium salts were prepared from the corresponding pyridinium salts in good yields as illustrated in the scheme.

In a typical procedure for the two-phase alkylation of active methylene compounds, a mixture of phenylacetonitrile (10) (234 mg, 2.0 mmol), ethyl bromide (262 mg, 2.4 mmol), and pyridinium salt 5 (19 mg, 0.04 mmol) was vigorously stirred with 50% aqueous sodium hydroxide (1.0 ml, 12.5 mmol) at room temperature for 24 hr. The resulting mixture was filtered by a short column packed with anhydrous sodium sulfate and silica gel, and the column was washed with dichloromethane. The filtrate and washings were concentrated to leave a mixture (270 mg) of mono- and dialkylated products (90% and 3%, estimated by nmr spectroscopy). The monoalkylated product (11)

Table Two-phase Alkylation Reaction Catalyzed with 2-Dialkylaminopyridinium Salts

Active methylene compound	Halide (eq.)	Catalyst (mol%)	Conditions temp.	time	solvent	Yield (%)* mono	di
10	C_2H_5Br (1.2)	none	70°C	7 hr		15	none
10	C_2H_5Br (1.2)	5 (1%)	70°C	5 hr		90	7
10	C_2H_5Br (1.2)	5 (2%)	r.t.	24 hr		90	3
10	C_2H_5Br (1.2)	6 (3%)	r.t.	48 hr		46	none
10	C_2H_5Br (1.2)	7 (3%)	50°C	8 hr		28	none
10	C_2H_5Br (1.2)	8 (2%)	r.t.	24 hr		37	none
10	C_2H_5Br (1.2)	9 (2%)	r.t.	24 hr		33	none
10	$PhCH_2Cl$ (1.0)	5 (1%)	r.t.	24 hr		63	14
10	$CH_2=CHCH_2Br$(1.3)	5 (3%)	r.t.	24 hr		63	34
10	^nBuBr (1.2)	5 (3%)	70°C	7 hr		65	6
10	^iPrBr (1.2)	5 (3%)	70°C	7 hr		23	none
11	CH_3Br(excess)	1 (3%)	r.t.	24 hr		96	—
11	CH_3Br(excess)	2 (4%)	r.t.	24 hr		63	—
11	CH_3Br(excess)	3 (3%)	r.t.	24 hr		93	—
11	CH_3Br(excess)	4 (4%)	r.t.	24 hr		89	—
11	CH_3Br(excess)	5 (3%)	r.t.	20 hr		93	—
11	CH_3Br(excess)	7 (3%)	r.t.	24 hr		quant.	—
11	CH_3Br(excess)	8 (2%)	r.t.	24 hr		69	—
11	$PhCH_2Cl$ (2.0)	3 (5%)	r.t.	24 hr		62	—
11	$PhCH_2Cl$ (2.0)	5 (2%)	r.t.	48 hr		81	—
11	$PhCH_2Br$ (2.0)	2 (4%)	r.t.	24 hr		quant.	—
11	$PhCH_2Br$ (2.0)	4 (4%)	r.t.	24 hr		quant.	—
11	$PhCH_2Br$ (2.0)	4 (3%)	r.t.	24 hr	hexane	quant.	—
11	$PhCH_2Br$ (2.0)	4 (3%)	r.t.	24 hr	benzene	36	—
11	$PhCH_2Br$ (2.0)	4 (3%)	r.t.	24 hr	ether	44	—
12	$PhCH_2Br$ (2.0)	5 (3%)	r.t.	24 hr		92	—
13	$PhCH_2Br$ (2.0)	none	r.t.	24 hr	$CHCl_3$	28	—
13	$PhCH_2Br$ (1.2)	1 (3%)	r.t.	24 hr	$CHCl_3$	92	—
13	$PhCH_2Br$ (2.0)	2 (4%)	r.t.	24 hr	$CHCl_3$	76	—
13	$PhCH_2Br$ (1.2)	3 (3%)	r.t.	24 hr	$CHCl_3$	86	—
13	$PhCH_2Br$ (2.0)	4 (4%)	r.t.	24 hr	$CHCl_3$	93	—
13	$PhCH_2Br$ (2.0)	4 (4%)	r.t.	24 hr	benzene	95	—
13	$PhCH_2Br$ (1.2)	5 (3%)	r.t.	24 hr	benzene	66	—
13	$PhCH_2Br$ (2.0)	8 (2%)	r.t.	24 hr	$CHCl_3$	92	—
13	$PhCH_2Br$ (2.0)	9 (2%)	r.t.	24 hr	$CHCl_3$	quant.	—
13	$CH_2=CHCH_2Br$(1.2)	5 (2%)	r.t.	24 hr	$CHCl_3$	57	—

* Each product gave satisfactory spectral data.

was isolated in 90% yield by preparative thin layer chromatography (hexane-benzene) or fractional distillation (117-118°C/21 mmHg). In the case of the two-phase alkylation of 2-ethoxycarbonylcyclopentanone (13), the reaction was carried out with 10% aqueous sodium hydroxide (1.0 ml/mmol) in such a suitable solvent as benzene or chloroform (1.0 ml/mmol). In similar manners, active methylene compounds 10 - 13 were successfully alkylated with various alkyl halides as summarized in the table.

The present catalysts, i.e. quaternary salts 3 - 9 and iminopyridine derivatives 1, 2, were found to accelerate the phase-transfer alkylation reaction although there were some differences in catalytic activities and substrate specificities as shown in the table. These alkylation reactions can be reasonably interpreted by the two-phase reaction mechanism.[1)]

It is noted that readily available 2-dialkylaminopyridinium salts are effective to catalyze the two-phase alkylation reaction under mild conditions. Further development focused on the asymmetric two-phase reaction[5)] with chiral catalysts is now in progress.

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