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CONVENIENT SYNTHESES OF PIPERAZINE-2,5-DIONES AND LACTAMS FROM HALOCARBOXAMIDES USING PHASE TRANSFER CATALYSTS

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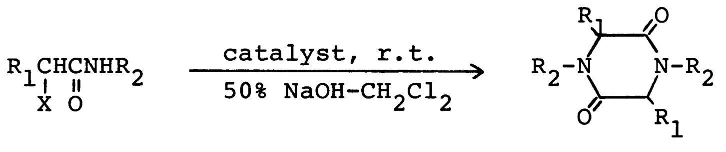
Inter- and intra-molecular N-alkylation of α-halocarboxamides and dihalocarboxamides in the presence of solid phase transfer catalyst led to the corresponding piperazine-2,5-diones (2) and lactams (4) in the yields of 64-88 and 63-99%, respectively. A one-pot synthesis of β-lactams (7) from α-methyl-α,β-dibromopropionyl chloride (5) and α-amino acid using phase transfer catalyst was also successfully achieved.

N-Alkylation of amides has generally been performed by treatment with metalic amide and hydride followed by alkyl halide. Recently, soluble phase transfer catalysts have been used to N-alkylation reaction of amides.[1-4] This method, however, has not hitherto been utilized to the synthesis of cyclic amides by inter- and intra-molecular reactions.

We now report convenient syntheses of piperazine-2,5-diones by intermolecular cyclization of α-halocarboxamides and lactams by intramolecular cyclization of dihalocarboxamides using a phase transfer catalyst. A solid phase transfer catalyst, commercially available strong base ion exchange resin, instead of soluble ones was employed, because the latter ones often make emulsion and the work-up difficult. The synthesis of piperazine-2,5-dione (2) was easily carried out by intermolecular N-alkylation of α-halocarboxamide (1) in a mixture of dichloromethane and 50% aqueous sodium hydroxide solution in the presence of strong base ion exchange resin (Duolite A-109 Cl^- form, polystyrene quarternary type I, Diamond Shamrock, Co.) in the yields of 64-88%. After stirring at room temperature for the period of time shown in Table 1, the organic solvent was separated and evaporated, and the residue was purified by recrystallization or silica gel column chromatography. The reaction conditions and the yields are summarized in Table 1.



1 2

Table 1. Preparation of Piperazine-2,5-diones (2)

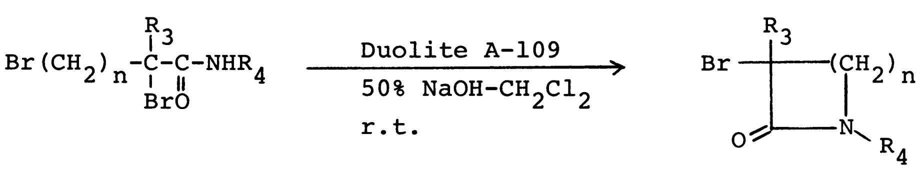
R_1	R_2	X	Catalyst	React.time (hr)	Temp.	Yield(%)	Mp(°C)
H	$PhCH_2$	Cl	none	24	r.t.	14	174-175
"	"	"	Duolite A-109	"	"	88	"
"	"	"	BTEAC[a)]	20	"	50	"
"	"	"	TBAI[b)]	24	"	46	"
"	Ph	"	Duolite A-109	18	"	64	266-267
CH_3	"	Br	"	24	"	64	155

All products gave satisfactory IR, ^{1}H-NMR, and Mass spectral data and elemental analyses.

a) Benzyltriethylammonium chloride. b) Tetrabutylammonium iodide.

The reaction is presumed to proceed by intermolecular cyclization. In the absence of the catalyst, 2 (R_1=H, R_2=$PhCH_2$) was obtained in a low yield. When soluble catalysts, benzyltriethylammonium chloride (BTEAC) and tetrabutylammonium iodide (TBAI), were used as the catalyst, considerably lower yields of 2 than using Duolite A-109 were obtained.

Recently, Kay reported the synthesis of α-methylene-β-lactam from N-aryl-3-bromo-2-bromoethylpropionamide using soluble catalysts.[5)] We tried intramolecular N-alkylation of N-phenyl- and N-benzyl-dibromocarboxamide (3) using the solid phase transfer catalyst, Duolite A-109, and obtained the corresponding lactams (4) in excellent yields.



3a-g 4a-g

The reaction conditions and the yields are shown in Table 2.

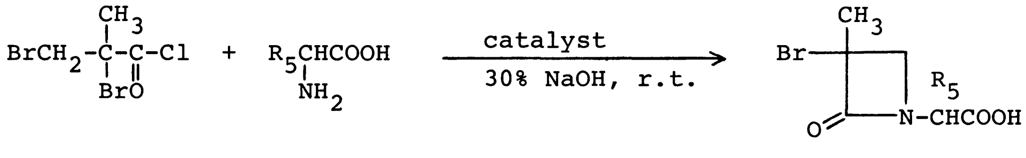
Table 2. Preparation of Lactams (4)

	n	R_3	R_4	Catalyst	React.time (hr)	Temp.	Yield(%)	Mp(°C) or Bp(°C/mmHg)
a	1	CH_3	Ph	Duolite A-109	4	r.t.	95	73
b	1	"	$PhCH_2$	none	100	"	26	oil
b	1	"	"	Duolite A-109	100	"	91	oil
b	1	"	"	BTEAC	100	"	93	oil
c	2	H	Ph	Duolite A-109	2.5	"	94	99
d	2	"	$PhCH_2$	"	25	"	96	171-172/0.9
e	3	"	Ph	"	5.5	"	98	84-85
f	3	"	$PhCH_2$	"	34	"	99	oil
g	4	"	Ph	"	95	"	63	211-213

All products gave satisfactory IR, ^{1}H-NMR, and Mass spectral data,and elemental analyses.

The possible formation of the corresponding piperazine-2,5-diones from 3 was not detected. The intramolecular N-alkylation of N-benzyl compounds (3b,d,and f) required prolonged reaction time more than that of N-phenyl compounds (3a,c,and e). In the absence of phase transfer catalysts, the intramolecular cyclization of 3b gave only 26% yield of the product even in prolonged reaction time. No difference between the effects of the soluble and solid catalysts was observed. While the compounds 3a and b not having α-hydrogen atom gave the β-lactams 4a and b in quantitative yields, N-phenyl-β-chloropropionamide (n=1, R_3=H, R_4=Ph) afforded only 5% yield of the corresponding β-lactam. In this case, concomitant β-elimination preferentially occurred.

The one-pot synthesis of β-lactam (7) from α-methyl-α,β-dibromopropionyl chloride (5) and (S)-phenylalanine or (R)-phenylglycine without isolating the intermediately formed amide was also successfully achieved in the yields of 45-65%.



5 6a-b 7a-b

The reaction was carried out in 30% aqueous sodium hydroxide solution without organic solvent in the presence of BTEAC. The lactams (7) were easily isolated by acidifying the reaction mixture with concentrated hydrochloric acid. The results are shown in Table 3.

Table 3. Preparation of Lactams (7)

7	R_5	Catalyst	React.time (hr)	Temp.	Yield(%)	Mp(°C)	$[\alpha]_D^{20}$ (c, solvent)
a	$PhCH_2$	BTEAC	24	r.t.	58	146	-31.5 (3.0, $CHCl_3$)$^{a)}$
a	"	Duolite A-109	"	"	65	b)	-12.1 (7.5, $CHCl_3$)$^{c)}$
b	Ph	BTEAC	"	"	45	149	-135.7 (3.4, $CHCl_3$)$^{a)}$

These products gave satisfactory IR, ^{1}H-NMR, and Mass spectral data,and elemental analyses.

a) The specific rotation after recrystallization from hexane-bezene. b) indefinite melting point, c) The integration intensity for ^{1}H-NMR spectrum of 7a without purification showed the same amount of the diastereomers.

This one-pot formation of β-lactam is worthy to note, because of simplicity of the method, and is currently under way.

References

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