

N-ALKYLATION OF LACTAMS WITH PHASE TRANSFER CATALYST<sup>1</sup>

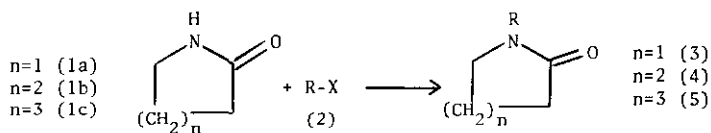
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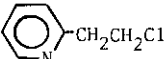
Abstract— N-Alkylation of lactams (1a,b,c) with alkyl halides (2) with phase transfer catalyst afforded various N-alkyl lactams (3,4, and 5) in good yields.

Reaction using phase transfer catalyst (PTC) has lately been versatile means for substitution, alkylation, carbene formation, oxidation, and so on.<sup>2</sup> However, there have been few papers for N-alkylation of the amide groups with PTC.<sup>3</sup> We now describe studies on N-alkylation of lactams (1a,b,c) in a heterogenous solid/liquid system.

In contrast to the precedents,<sup>4</sup> a versatile and mild procedure for the preparation of N-substituted lactams was realized by the use of a solid/liquid two phase system consisting of pulverized KOH and THF as a solvent together with tetrabutylammonium bromide (TBAB).



(2) R-X, a) CH<sub>3</sub>I, b) n-BuBr, c) n-BuCl, d) sec-BuBr, e) NCCH<sub>2</sub>CH<sub>2</sub>Cl, f) (MeO)<sub>2</sub>CHCH<sub>2</sub>CH<sub>2</sub>Cl

g) PhCH<sub>2</sub>Br, h) PhCH<sub>2</sub>CH<sub>2</sub>Br, i) 

General procedure for N-alkylation— A solution of 2 (0.05 mol) and 1 (0.05 mol) in 20 ml of dry THF was added to a suspension of pulverized KOH (0.055 mol) and TBAB (0.01 mol) in 50 ml of dry THF over 1 hr at room temperature. After completion of addition, the reaction mixture (2, X=Br,I) was stirred for 3-7 hr at room temperature. On the other hand, the reaction mixture (2, X=Cl) required a reflux for 2-3 hr. The precipitate was filtered off and the filtrate was evaporated in vacuo to leave an oil, to which was added CH<sub>2</sub>Cl<sub>2</sub> and H<sub>2</sub>O. The organic phase was washed with saturated aqueous NaCl and dried over anhydrous MgSO<sub>4</sub>. Removal of the solvent under reduced pressure gave 3,4, and 5.

Table 1. Formation of N-Substituted Lactams<sup>a</sup>

Products	Yield (%) <sup>b</sup>	Condition <sup>c</sup>	b.p./torr	Lit. b.p./torr	I.R. (neat)
			or m.p. (°C)	or m.p. (°C)	$\nu$ c=O (cm <sup>-1</sup> )
3a	92 (93) <sup>d</sup>	r.t. 3 hr	76/10	202/760 <sup>5</sup>	1660
4a	95 (92) <sup>d</sup>	r.t. 3 hr	97/10	108/18 <sup>5</sup>	1650
5a	96	r.t. 3 hr	75/2	75/1.7 <sup>6</sup>	1640
3b	85 (71) <sup>e</sup>	r.t. 4 hr	105/10	121/16 <sup>5</sup>	1660
4b	82	r.t. 4 hr	135/11	131/11 <sup>5</sup>	1660
5b	79	r.t. 5 hr	101/1	121/5 <sup>6</sup>	1640
3c	90 (55) <sup>e</sup>	refl. 2 hr	_____	_____	_____
4c	85	refl. 2 hr	_____	_____	_____
5c	87 (82) <sup>d</sup>	refl. 3 hr	_____	_____	_____
3d	71	r.t. 7 hr	101/12	101/8 <sup>7</sup>	1650
4d	65	r.t. 7 hr	75/2.5	_____	1640
5d	66	r.t. 7 hr	38	_____	1640 <sup>f</sup>
3e	71 (72) <sup>d</sup>	refl. 3 hr	140/2	121/0.1 <sup>8</sup>	1660
4e	70	refl. 3 hr	147/2.5	_____	1640
3f	70	refl. 3 hr	110/0.4	_____	1640
4f	69	refl. 3 hr	105/0.1	_____	1640
3g	89	r.t. 4hr	140/2	144/3 <sup>9</sup>	1660
4g	91	r.t. 4 hr	156/4	193/8 <sup>5</sup>	1640
3h	45	r.t. 5 hr	140/2	105/0.05 <sup>10</sup>	1660
4h	38	r.t. 6 hr	43	45 <sup>11</sup>	1660 <sup>f</sup>
3i	45	refl. 3 hr	65	_____	1660 <sup>f</sup>

a) All new products exhibited the expected pmr, ms, and analytical data.

b) Isolated yields after distillation.

c) THF was used as a solvent.

d) CH<sub>3</sub>CN was used as a solvent.

e) CH<sub>2</sub>Cl<sub>2</sub> was used as a solvent.

f) I.R. (nujol).

The results are summarized in Table 1. The reaction time increases with decreasing amount of catalyst TBAB<sup>12</sup>, and in the absence of catalyst, practically the reaction gave 3b (9%) and 3c (5%) in low yields. Primary halides react faster than secondary ones, and bromides are more reactive than chlorides. The replacement of THF with CH<sub>3</sub>CN caused no changes in yields of the products, but the use of CH<sub>2</sub>Cl<sub>2</sub> as a solvent caused decrease in yield.

Next, the compounds (3e and 3f) and (4e and 4f) were used as synthons for the syntheses of 8,13- and 5,9-diazasteroids, respectively.<sup>13</sup> We are currently investigating intramolecular N-alkylation of β-halopropionamides with phase transfer catalyst and a useful synthesis of monocyclic β-lactams will be reported soon.

#### References and Notes

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Received, 10th August, 1979