N-ALKYLATION OF LACTAMS WITH PHASE TRANSFER CATALYST[1]

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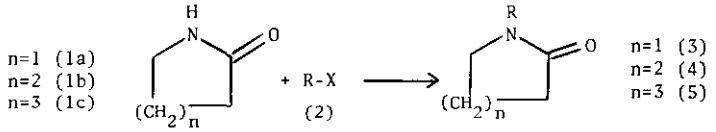
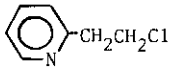
Abstract—— N-Alkylation of lactams (1a,b,c) with alkyl halides (2) with phase transfer catalyst afforded various N-alkyl lactams (3,4, and 5) in good yields.

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

In contrast to the precedents,[4] 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_3I, b) n-BuBr, c) n-BuCl, d) sec-BuBr, e) $NCCH_2CH_2Cl$, f) $(MeO)_2CHCH_2CH_2Cl$
g) $PhCH_2Br$, h) $PhCH_2CH_2Br$, 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_2Cl_2 and H_2O. The organic phase was washed with saturated aqeuous NaCl and dried over anhydrous $MgSO_4$. Removal of the solvent under reduced pressure gave 3,4, and 5.

Table 1. Formation of N-Substituted Lactams[a]

Products	Yield (%)[b]	Condition[c]	b.p,/torr or m.p. (°C)	Lit. b.p./torr or m.p. (°C)	I.R. (neat) ν c=o (cm^{-1})
3a	92 (93)[d]	r.t. 3 hr	76/10	202/760[5]	1660
4a	95 (92)[d]	r.t. 3 hr	97/10	108/18[5]	1650
5a	96	r.t. 3 hr	75/2	75/1.7[6]	1640
3b	85 (71)[e]	r.t. 4 hr	105/10	121/16[5]	1660
4b	82	r.t. 4 hr	135/11	131/11[5]	1660
5b	79	r.t. 5 hr	101/1	121/5[6]	1640
3c	90 (55)[e]	refl. 2 hr	———	———	———
4c	85	refl. 2 hr	———	———	———
5c	87 (82)[d]	refl. 3 hr	———	———	———
3d	71	r.t. 7 hr	101/12	101/8[7]	1650
4d	65	r.t. 7 hr	75/2.5	———	1640
5d	66	r.t. 7 hr	38	———	1640[f]
3e	71 (72)[d]	refl. 3 hr	140/2	121/0.1[8]	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[9]	1660
4g	91	r.t. 4 hr	156/4	193/8[5]	1640
3h	45	r.t. 5 hr	140/2	105/0.05[10]	1660
4h	38	r.t. 6 hr	43	45[11]	1660[f]
3i	45	refl. 3 hr	65	———	1660[f]

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_3CN was used as a solvent.

e) CH_2Cl_2 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[12], 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_3CN caused no changes in yields of the products, but the use of CH_2Cl_2 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.[13] 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