N-ALKYLATION OF AZETIDIN-2-ONES WITH PHASE TRANSFER CATALYSIS

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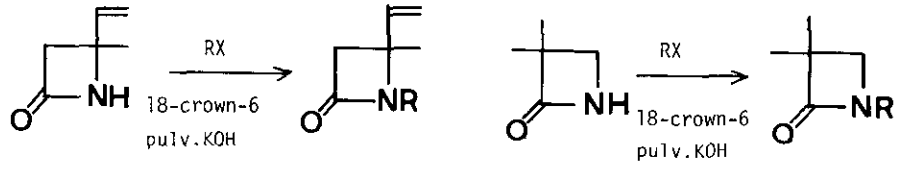
Abstract ---- Various N-alkyl azetidin-2-ones were prepared by using 18-crown-6 catalysis involving pulverized KOH, azetidin-2-one derivatives, and alkyl halides in benzene in good yield.

N-Alkylation of 1-unsubstituted azetidin-2-ones is one of the important steps to the synthesis of the β-lactam antibiotics.[1] The reaction has hitherto been conducted in the presence of a strong base, such as sodium amide in liquid ammonia or sodium hydride.[2] Recently, there have been seen some reports on the N-alkylation of the amide groups with PTC.[3] We wish here to report the studies on the N-alkylation of azetidin-2-one (1) and (2) using phase transfer catalysis with 18-crown-6.



(1) (2a-1) (3) (4c-i)

R-X, a) CH_3I, b) CH_3CH_2Br, c) n-C_3H_7Br, d) n-C_4H_9Br, e) $C_6H_5CH_2Br$, f) $C_6H_5CH_2CH_2Br$
g) $(CH_3O)_2CHCH_2CH_2Cl$, h) THPO∿∿Br, i) HO∿∿Br, j) THFO∿Br, k) HO∿Br, l) $ClCH_2CO_2CH_3$

A general procedure is as follows; a solution of n-propyl bromide(1g, $9x10^{-3}$mol) in 10 ml of benzene was added to a suspension of pulverized KOH(0.72g, $9.9x10^{-3}$mol), 18-crown-6(0.05g, $2x10^{-5}$ mol), and (1)[4] in 10 ml of benzene over 30 min at room temperature, and the reaction mixture was stirred for 2h. The precipitate was filtered off and 10 ml of H_2O was added to the filtrate. The benzene layer was separated and dried over anhydrous $MgSO_4$. Then the solvent was distillated off to yield 1.32g($8.7x10^{-3}$mol, 96%) of oil(2a)[ν_{max}^{KBr} 1750 cm^{-1}, δ($CDCl_3$) 0.90(3H, t, J=6Hz), 1.20-1.83(2H, m), 1.50(3H, s), 2.80(2H, s), 2.97(2H, t, J=7Hz), 5.24(1H, dd, J=10 and 1.5Hz), 5.25(1H, dd, J=18 and 1.5Hz), 6.60(1H, dd, J=18 and 10Hz)].[5]

Table 1. Formation of N-Alkylated Azetidin-2-one

Product	Condition				Yield
2c	refl.	2h	KH	THF	90%
2c	60°	3h	pluv.KOH	CCl_4	45%
2c	r.t.	3h	pluv.KOH	MeCN	68%
2c	r.t.	2h	pluv.KOH	Benzene	96%
2a	r.t.	2h	pluv.KOH	Benzene	86%
2b	r.t.	2h	pluv.KOH	Benzene	89%
2d	r.t.	2h	pluv.KOH	Benzene	94%
2e	r.t.	1h	pluv.KOH	Benzene	98%
2f	r.t.	3h	pluv.KOH	Benzene	44%
2g	60°	12h	pluv.KOH	Benzene	38%
2h	60°	12h	pluv.KOH	Benzene	62%
2j	60°	12h	pluv.KOH	Benzene	59%
2l	r.t.	1h	pluv.KOH	Benzene	69%
4c	r.t.	2h	Pluv.KOH	Benzene	89%
4d	r.t.	2h	Pluv.KOH	Benzene	91%
4h	60°	12h	pluv.KOH	Benzene	56%
4l	60°	12h	pluv.KOH	Benzene	54%

Our results are summarized in Table I. The reaction time is elongated with the decrease in the amount of 18-crown-6, and in the absence of the catalyst the reaction did not proceed. With regard to the solvent employed, the N-alkylated β-lactams could be prepared in good yield by using benzene. The procedure is simple, straigtforwared and very easy to work up.[6] Next, N-alkylazetidin-2-ones(4h) and (4j) were easily hydrolyzed (5%-HCl-aqueous methanol solution) to hydroxy compounds(4i)(92%) and (4k)(90%),which would be expected useful compounds for the syntheses of 1-oxacephems.[7] We expect to further develop this method for N-alkylation of azetidin-2-one having asymmetric center on 2 or 3 position.

REFERENCE AND NOTE

1. N-Alkylation was used to prepare β-lactams exhibiting sedative, central depressant, and anti-convulsive activity.; Calanda-Stiftung, British Patent, 1963, 924589; C.A., 1963, 59, 11424.

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5. Satisfactory elemental analyses were obtained on new compounds.

6. N-Alkylation of azetidin-2-one employing tetrabutylammonium bromide was reported.[3c] Our procedure is milder, requiers much less catalyst(2×10^{-5}eq.) and give comparable yield.

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