

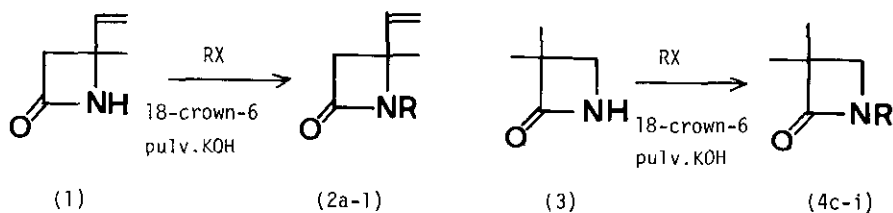
N-ALKYLATION OF AZETIDIN-2-ONES WITH PHASE TRANSFER CATALYSIS

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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.



R-X, a) CH_3I , b) $\text{CH}_3\text{CH}_2\text{Br}$, c) $n\text{-C}_3\text{H}_7\text{Br}$, d) $n\text{-C}_4\text{H}_9\text{Br}$, e) $\text{C}_6\text{H}_5\text{CH}_2\text{Br}$, f) $\text{C}_6\text{H}_5\text{CH}_2\text{CH}_2\text{Br}$
 g) $(\text{CH}_3\text{O})_2\text{CHCH}_2\text{CH}_2\text{Cl}$, h) $\text{THPO}\text{---}\text{Br}$, i) $\text{HO}\text{---}\text{Br}$, j) $\text{THFO}\text{---}\text{Br}$, k) $\text{HO}\text{---}\text{Br}$, l) $\text{ClCH}_2\text{CO}_2\text{CH}_3$

A general procedure is as follows; a solution of n-propyl bromide (1g, 9×10^{-3} mol) in 10 ml of benzene was added to a suspension of pulverized KOH (0.72g, 9.9×10^{-3} mol), 18-crown-6 (0.05g, 2×10^{-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 distilled off to yield 1.32g (8.7×10^{-3} mol, 96%) of oil (2a) [$\nu_{\text{max}}^{\text{KBr}}$ 1750 cm^{-1} , $\delta(\text{CDCl}_3)$ 0.90(3H, t, $J=6\text{Hz}$), 1.20-1.83(2H, m), 1.50(3H, s), 2.80(2H, s), 2.97(2H, t, $J=7\text{Hz}$), 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%
4i	60°	12h	pluv.KOH	Benzene	54%

Our results are summarized in Table 1. 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, straightforward 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

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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, requires much less catalyst(2×10^{-5} eq.) and give comparable yield.
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Received, 6th October, 1980