β-Lactam Formation by Ultrasound-promoted Reformatsky Type Reaction†

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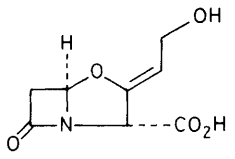
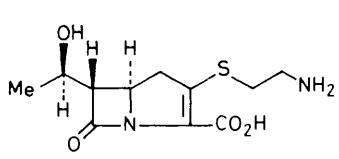
Ultrasound was found to promote the reaction between ethyl bromoacetate, zinc, and a Schiff base such that an excellent yield of β-lactams was obtained in a few hours at room temperature.

Most β-lactam antibiotics found in nature are characterized by an α-amido or an α-methanol side chain. Clavulanic acid (**1**) and related antibiotics[1] constitute so far the only β-lactam family that carries no substituent on the carbon adjacent to the β-lactam carbonyl. This type of β-lactam has been utilized recently as an intermediate in the preparation of thienamycin (**2**) and analogues.[2]

Of the few direct synthetic approaches to α-unsubstituted β-lactams, the Reformatsky type reaction of Gilman and Speeter[3] (Scheme 1) is of considerable interest. During the last few years reports have appeared indicating the value of ultrasound in promoting chemical reactions, especially those involving organometallic reagents. Specifically, Han and Boudjouk[4] have observed beneficial effects of ultrasonic irradiation on the Reformatsky reaction. Therefore, we have examined the possibility of promoting Gilman and Speeter's synthesis with ultrasound. Our observations are reported here.



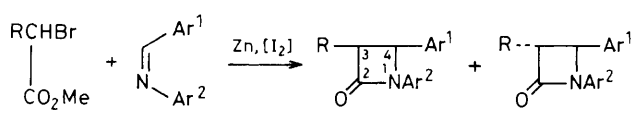
(**1**)



(**2**)

We duplicated the reaction conditions used earlier,[3] namely, reaction of ethyl bromoacetate and a Schiff base in the presence of zinc and a crystal of iodine as a catalyst. In refluxing toluene the reaction proceeded slowly and the yield of β-lactam was 25—50%. A recent report[5] described somewhat higher yields (50—70%) by using pure zinc foil.

As a convenient source of ultrasound we employed a commercially available cleaning bath filled with water. In the light of the observation of Han and Boudjouk[4] that dioxane is better than the common Reformatsky solvents, *viz.*, diethyl ether and benzene, when sonication is used, we substituted dioxane for toluene as the reaction medium. Under these conditions‡ β-lactam formation occurred even at room temperature. Activated zinc granules led in a few hours to as high



Scheme 1

† For part 68 of the series 'Studies on Lactams' see M. S. Manhas, M. S. Khajavi, S. S. Bari, and A. K. Bose, *Tetrahedron Lett.*, 1983, **24**, 2323.

‡ A water filled ultrasonic laboratory cleaner (Cole Parmer) was used for irradiating the reaction mixture of Schiff base, activated zinc (HNO_3 washed), ethyl bromoacetate, and a crystal of iodine. The reaction progress was monitored by t.l.c. All new compounds were characterized by satisfactory spectral and elemental analyses.

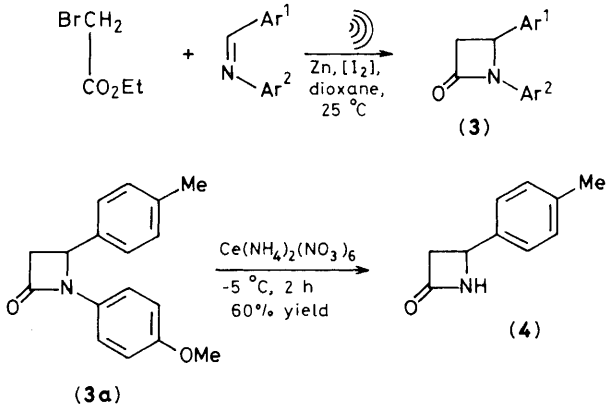


Table 1. Ultrasound-promoted Reformatsky type reaction.

Product	Ar^1	Ar^2	Reaction time/h	Yield of (3) %
(3a)	C_6H_4Me-*p*	C_6H_4OMe-*p*	4	95
(3b)	C_6H_4Me-*p*	C_6H_4OMe-*p*	10	85
(3c)	Ph	C_6H_4OMe-*p*	5	82
(3d)	Ph	Ph	5	70
(3e)	C_6H_4Cl-*p*	C_6H_4OMe-*p*	6	77

as 90% yield of β-lactams (Table 1) while unactivated zinc granules gave a lower yield (50—70%). Surprisingly, the substitution of α-bromopropionic or α-bromo-β-phenylpropionic esters for bromoacetic ester failed to produce any β-lactam§[6] although most of the reactants were consumed.

Recently the oxidative removal of the *N*-(*p*-methoxyphenyl) group by cerium(III) ammonium nitrate has been described.[7] The application of this approach to β-lactam (**3a**) prepared by us led in 60% yield to the *N*-unsubstituted β-lactam (**4**). This type of compound can serve as the starting material for a variety of substituted β-lactams since methods are known for introducing substituents on the β-lactam nitrogen and at C-3.

The mechanism of the Reformatsky reaction is not fully understood.¶ Studies are in progress in our laboratory using ^{13}C- and ^{15}N-labelled starting materials to determine the mechanism of β-lactam formation by Gilman and Speeter's method.

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§ Mixtures of *cis*- and *trans*-(3-substituted)azetidin-2-ones have been prepared by previous workers (refs. 3, 6) using conventional Reformatsky reaction conditions.

¶ For example, a recent publication (ref. 8) has revealed for the first time that both in the solid state and tetrahydrofuran (THF) solution, the Reformatsky reagent from t-butyl bromoacetate is an 8-membered non-planar ring containing two zinc atoms surrounded tetrahedrally by two oxygen (ester carbonyl, THF), one bromine, and one carbon atom (CH_2 of acetic acid).