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DMF-dimethyl sulfate as a new reagent for the synthesis of β-lactams

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ABSTRACT

A number of 2-azetidinones were synthesized in good to excellent yields by a novel reaction between Schiff bases, substituted acetic acids and alkoxymethylene-*N,N*-dimethyliminium salts, the adduct formed from DMF and O-alkylating agents. The advantages of this new method are mild reaction conditions, low cost, avoiding the use of chlorinating agents and easy purification of the products. The best results were obtained when DMF and dimethyl sulfate were used at room temperature.

Due to their excellent safety profile and broad spectrum of action, β-lactam antibiotics remain among the most commonly prescribed antimicrobial products. However, antibiotic-resistant strains are arising at an alarming rate.[1] The biological properties of 2-azetidinones make them attractive research targets.[2] Additional impetus for research efforts on β-lactam chemistry was provided by the introduction of the β-lactam synthon method, a term coined by Ojima,[3] and according to which, 2-azetidinones can be employed as useful intermediates in organic synthesis.[4] It is therefore no surprise that chemical methods leading to the direct and facile synthesis of β-lactams remain important.[5] First reported by Staudinger, the cycloaddition reaction of ketenes with imines is a versatile and efficient route to construct β-lactams.[6]

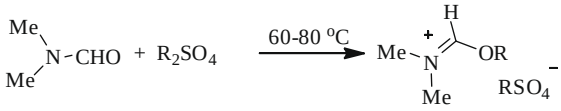
Although a number of methods for the preparation of ketenes have been introduced,[7] the reaction of acyl halides with tertiary amines is commonly used.[8] However, in a number of cases, the use of acyl halides produces poor results, for example, when ketenes from acyl halides contain strong electron withdrawing groups, low yields of the corresponding β-lactams are obtained.[9] Sometimes, the acid halides are not commercially available and they are prepared from carboxylic acids and halogenating agents such as $POCl_3$, $SOCl_2$ and $(COCl)_2$.

One of the most versatile methods for the one-step construction of the 2-azetidinone ring is the reaction between an activated carboxylic acid and an imine in the presence of a tertiary base.[10] 2-Chloro-1,3-dimethylimidazolinium chloride,[11] 1,1-carbonyldi-imidazole,[12] triphosgene,[13] ethyl chloroformate,[14] trifluoroacetic anhydride,[15] *p*-toluenesulfonyl chloride,[16] phosphorus derived reagents,[17] cyanuric chloride,[18] the Mukaiyama reagent,[19] acetic anhydride,[20] Lawesson's reagent[21] and the Vilsmeier reagent[22] (DMF and $SOCl_2$ or $(COCl)_2$) are acid activators that have been used previously in the synthesis of β-lactams. The high cost, poor availability, pollution and low yields are some disadvantages of these acid activators.

Alkoxymethylene-*N,N*-dimethyliminium salts are prepared by reaction of DMF and O-alkylating agents such as trialkyloxonium salts,[23] alkyl sulfates[24] or by reaction of DMF, an epoxide and an acid.[25] These compounds are used in the synthesis of 3-acylated indolizines,[26] catalysis of the Beckmann rearrangement[27] and preparation of benzylidene acetals of mono- and disaccharides.[28] To the best of our knowledge, these salts have never been used in β-lactam synthesis.

The objective of this work was to investigate the application of alkoxymethylene-*N,N*-dimethyliminium salts as useful reagents for the synthesis of β-lactams.

Methoxy- and ethoxy-methylene-*N,N*-dimethyliminium salts **1a–b** were prepared by reacting *N,N*-dimethylformamide (DMF) with Me_2SO_4 and Et_2SO_4, respectively, (Scheme 1). Me_2SO_4 and Et_2SO_4 are toxic so the reaction must be carried out in a hood.



Scheme 1.

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Salts **1a–b** in DMF were used (after cooling) without any further purification. To characterize the structure of **1a**, excess DMF was removed under reduced pressure and a gel-like solid was obtained. The IR spectrum showed a characteristic absorption due to the C=N group at 1721 cm^{-1}. The iminium salts **1a** or **1b** were added to a solution of various imines and carboxylic acids in dry dichloromethane. As is shown in Table 1, DMF or Me_2SO_4 alone was inactive. Salt **1a** (DMF/Me_2SO_4) showed better activity than **1b** (DMF/Et_2SO_4) in the synthesis of β-lactams (Scheme 2). Also, the yields were better at room temperature than at 0 °C.

Based on the above results, 2-azetidinones **2a–l** were synthesized by treatment of 1.0 mmol of imine, 1.5 mmol of substituted acetic acid and 1.5 mmol of **1a** in the presence of triethylamine in dry dichloromethane at room temperature for 9–13 h (Table 2). The reactions were very clean, simple and efficient. A simple aqueous work-up removed DMF and salts.

The pure β-lactams **2a–h** and **2k–l** were obtained by crystallization from EtOAc. The crotonic acid (2-butenoic acid) and derived β-lactams **2i–j** were purified by short silica gel column chromatography. The stereochemistry of the products depended on the electronic effects and the steric hindrance of the carboxylic acid and imine substitutents.[29] The cis and trans stereochemistries of 2-azetidinones **2a–l** were deduced from the coupling constants of H-3 and H-4, which were calculated to be greater than 4.0 for the cis isomers and less than 2.5 for the trans isomers.

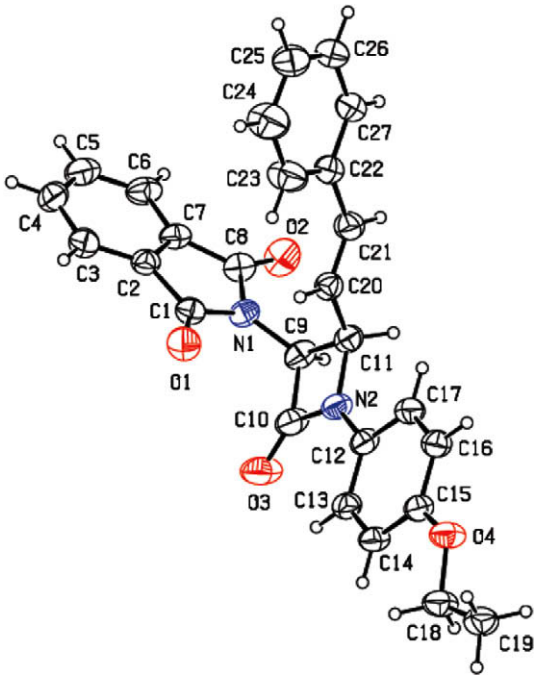
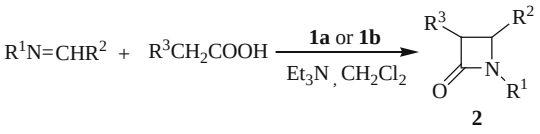


Figure 1. ORTEP diagram of β-lactam **2g**.[30]

Table 1
Reaction conditions for the synthesis of **2a–b**

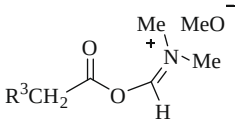
R^1	R^2	R^3	Reagent	Temp.	Product	Yield (%)
4-$MeOC_6H_4$	4-MeC_6H_4	PhO	DMF	rt	—	—
4-$MeOC_6H_4$	4-MeC_6H_4	PhO	Me_2SO_4	rt	—	—
4-$MeOC_6H_4$	4-MeC_6H_4	PhO	**1a**	0 °C	**2a**	31
4-$MeOC_6H_4$	4-MeC_6H_4	PhO	**1a**	rt	**2a**	87
4-$MeOC_6H_4$	4-MeC_6H_4	PhO	**1b**	0 °C	**2a**	26
4-$MeOC_6H_4$	4-MeC_6H_4	PhO	**1b**	rt	**2a**	49
4-$EtOC_6H_4$	4-$NO_2C_6H_4$	MeO	**1a**	0 °C	**2b**	53
4-$EtOC_6H_4$	4-$NO_2C_6H_4$	MeO	**1a**	rt	**2b**	82
4-$EtOC_6H_4$	4-$NO_2C_6H_4$	MeO	**1b**	0 °C	**2b**	18
4-$EtOC_6H_4$	4-$NO_2C_6H_4$	MeO	**1b**	rt	**2b**	44



Scheme 2.

All the products were characterized from spectral data and elemental analyses. The structure of β-lactam **2g** was further confirmed by a single-crystal X-ray analysis (Fig. 1).

We suggest that the reaction proceeds via formation of an activated form of the carboxylic acid **3** that undergoes deprotonation and loss of DMF to generate the corresponding ketene.



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In conclusion, alkoxymethylene-*N*,*N*-dimethyliminium salts, which were easily prepared from common reagents, are effective reagents for the one-pot synthesis of β-lactams from imines and acetic acid derivatives under mild conditions.[31] The low cost of DMF/Me_2SO_4 (**1a**) and the high yield of products make DMF/Me_2SO_4 an attractive reagent for the synthesis of β-lactams.

Table 2
Synthesis of 2-azetidinones using reagent **1a**

Entry	R^1	R^2	R^3	Product	Cis/trans	Isolated yield (%)
1	4-$MeOC_6H_4$	4-MeC_6H_4	PhO	**2a**	Cis	87
2	4-$EtOC_6H_4$	4-$NO_2C_6H_4$	MeO	**2b**	Cis	82
3	4-$EtOC_6H_4$	4-ClC_6H_4	PhO	**2c**	Cis	91
4	4-$MeOC_6H_4$	4-ClC_6H_4	MeO	**2d**	Cis	85
5	4-$EtOC_6H_4$	4-$NO_2C_6H_4$	2,4-$Cl_2C_6H_3O$	**2e**	Cis	94
6	4-$MeOC_6H_4$	4-ClC_6H_4	2,4-$Cl_2C_6H_3O$	**2f**	Cis	79
7	4-$EtOC_6H_4$	CH=CHPh	PhthN	**2g**	Cis	90
8	4-$EtOC_6H_4$	4-$MeOC_6H_4$	PhthN	**2h**	Cis	82
9	4-$MeOC_6H_4$	4-$MeOC_6H_4$	CH_2=CH	**2i**	Trans	58
10	4-$EtOC_6H_4$	4-$NO_2C_6H_4$	CH_2=CH	**2j**	Trans	64
11	4-$EtOC_6H_4$	4-$MeOC_6H_4$	2-Naphthyloxy	**2k**	Cis	94
12	4-$EtOC_6H_4$	4-$NO_2C_6H_4$	2-Naphthyloxy	**2l**	Cis	88

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31. *General procedure*: A mixture of *N,N*-dimethylformamide (1.7 mmol) and Me_2SO_4 or Et_2SO_4 (1.5 mmol) was stirred at 60–80 °C for 2 h. [In the case of DMF/Me_2SO_4 by removal of excess DMF and addition of 2 ml of $CHCl_3$: IR cm^{-1} 1246, 1068 (C–O–C) and 1721 (C=N)]. After cooling to room temperature, the resulting solution was added to a mixture of imine (1.0 mmol) and substituted acetic acid (1.5 mmol) in dry dichloromethane. The reaction mixture was stirred for 10–15 min, and then dry triethylamine (5.0 mmol) was added at 0 °C or at room temperature and the reaction mixture was stirred overnight at room temperature. The solution was washed successively with 10% HCl (20 ml), saturated $NaHCO_3$ (20 ml) and brine (20 ml), dried over Na_2SO_4 and then filtered. The solvent was evaporated under reduced pressure to give the crude product. β-Lactams **2a**–**h**, **2k**–**l** were purified by crystallization from ethyl acetate and β-lactams **2i**–**j** by short column chromatography. *2-(1-(4-Ethoxyphenyl)-2-oxo-4-styryl-azetidin-3-yl)isoindoline-1,3-dione* (**2g**). Yield: 90% mp: 160–162 °C; IR ($CHCl_3$) cm^{-1}: 1726, 1756 (CO, phth), 1778 (CO, β-lactam); ^1H NMR (250 MHz, $CDCl_3$) δ 1.37 (Me, t, 3H, J = 6.9), 3.97 (OCH_2, q, 2H, J = 6.8), 5.03 (H-4, dd, 1H, J = 5.5, 8.5), 5.68 (H-3, d, 1H, J = 5.5), 6.32 (H-5, dd, 1H, J = 8.5, 16.0), 6.85 (H-6, d, 1H, J = 16.0), 7.19–7.82 (ArH, m, 13H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 14.8 (Me), 57.7 (OCH_2), 61.0 (C-4), 63.7 (C-3), 115.0–155.8 (C=C, aromatic carbons), 160.6 (CO, phth), 167.3 (CO, β-lactam); GC–MS m/z = 438 [M^+]; Anal. Calcd for $C_{27}H_{22}N_2O_4$: C, 73.96; H, 5.06; N, 6.39. Found: C, 74.02; H, 5.09; N, 6.33.