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A straightforward approach to 2-azetidinones from imines and carboxylic acids using dimethyl sulfoxide and acetic anhydride

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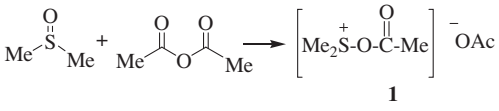
ABSTRACT

The direct synthesis of 2-azetidinones from imines and carboxylic acids under mild conditions is developed. Dimethyl sulfoxide (DMSO) can be activated by acetic anhydride and the resulting active species is used for the in situ generation of ketenes from carboxylic acids. This method is cheap, simple, convenient, and efficient and the products are easily isolated.

As examples of very important heterocyclic compounds, β-lactams (2-azetidinones) have been considered as privileged structures in chemical, pharmaceutical, and materials industries.[1] The β-lactam antibiotics, including penicillins, cephalosporins, monobactams, and carbapenems, are often administered because of their wide spectrum of activity, safety, and reliable clinical efficacy.[2] Unfortunately, resistance against the common β-lactam antibiotics has increased,[3] and interest in creating new β-lactam antibiotics and new methods for the synthesis of β-lactams is rising. 2-Azetidinones have been shown to possess a wide variety of pharmacological activities,[4] for example, ezetimibe is used clinically due to its cholesterol absorption inhibitor property.[5] In addition, 2-azetidinones are used as intermediates in the synthesis of many classes of compounds[6] and in the semi-synthesis of taxol derivatives.[7]

Many different methods have been developed for the formation of the 2-azetidinone ring.[8] Despite Staudinger reporting the reaction between ketenes and imines in 1907,[9] undoubtedly this reaction is the most widely used route, which can be used for the synthesis of several types of 2-azetidinones.[10]

Ketenes are typically generated by the reaction of acyl halides with tertiary amines,[11] but the preparation, isolation, and handling of acid chlorides are difficult and they are unstable. Activation of carboxylic acids for the formation of amide or ester bonds is a key step in the synthesis of a large number of bioorganic molecules.[12] 2-Azetidinones can also be synthesized by the one-pot reaction of in situ activated carboxylic acids and imines.[13] Low yields, harsh conditions, and chromatographic separations are the disadvantages of some of these activated acids.



1

Scheme 1.

Dimethyl sulfoxide (DMSO) can be activated by acetic anhydride and the resulting species **1** (Scheme 1) has been used for the synthesis of nitriles from aldoximes[14] and the oxidation of alcohols.[15]

On this basis and following interest in the use of acid activators for the synthesis of 2-azetidinones, herein a mild and efficient alternative procedure for the conversion of imines and carboxylic acids into the corresponding 2-azetidinones is reported.

At first, the reaction of imine **2a** and phenoxyacetic acid in DMSO in the presence of triethylamine at room temperature was examined, but no reaction was observed after 13 h. When acetic anhydride was added to this mixture at room temperature, TLC monitoring showed that a reaction took place to give 2-azetidinone **4a** (Table 1, entry 2) after purification by column chromatography. Reaction in dichloromethane as the solvent at room temperature in the absence of DMSO (entry 3) gave no reaction. These initial

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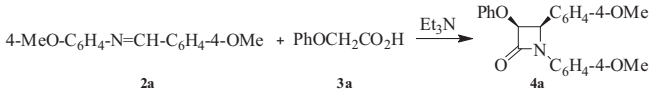
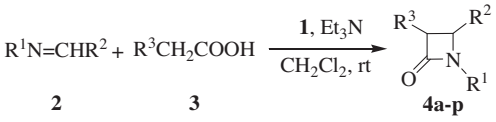
Table 1
Optimization of the reaction conditions for the synthesis of 2-azetidinone **4a**



Entry	Reagent (mmol)	Solvent	Temp	Yield (%)
1	–	DMSO	rt	–
2	Ac_2O (1.0)	DMSO	rt	43
3	Ac_2O (1.0)	CH_2Cl_2	rt	–
4	**1** (1.0)	CH_2Cl_2	rt	61
5	**1** (1.0)	CH_3CN	rt	29
6	**1** (1.0)	THF	rt	37
7	**1** (1.0)	Toluene	rt	45
8	**1** (1.3)	CH_2Cl_2	rt	83
9	**1** (1.5)	CH_2Cl_2	rt	91
10	**1** (2.0)	CH_2Cl_2	rt	89
11	**1** (1.5)	CH_2Cl_2	0 °C	85



Scheme 2.

results show that DMSO and acetic anhydride together activate the carboxylic acid. Treatment of imine **2a**, phenoxyacetic acid, and triethylamine in the presence of Ac_2O and DMSO at room temperature in dry dichloromethane afforded the corresponding 2-azetidinone in 61% yield. Hence, different conditions were examined in order to find the optimum parameters and the results are summarized in Table 1.

The best result was obtained using DMSO and Ac_2O (1.5 mmol) in CH_2Cl_2 at room temperature in the presence of Et_3N (91% yield, entry 9).

Next, the ability of DMSO and Ac_2O to activate various acetic acid derivatives was investigated for the synthesis of a range of 2-azetidinones (Scheme 2, Table 2).

As can be seen from Table 2, this method was applied for the conversion of a range of carboxylic acids and imines into the corresponding 2-azetidinones in good to excellent yields.[16] 2-Azetidinones **4j–l** which contain aliphatic substituents can also be synthesized by this method. The lower stability of alkyl-substituted imines compared to aryl-substituted imines led to lower yields of 2-azetidinones **4k–l**. In particular, 2-azetidinone **4l** was obtained in a poor yield because of the lower stability of the imine derived from an aliphatic amine and an aldehyde. Heteroaromatic-substituted 2-azetidinone **4m** was also prepared in good yield using activated DMSO. Activated DMSO was successfully employed for the synthesis of C-3 spiro-2-azetidinones **4n–p** by the cycloaddition reaction of xanthene-9-carboxylic acid with Schiff bases in the presence of activated DMSO.

2-Azetidinones **4a–p** were purified by crystallization from EtOAc after simple aqueous work-up. This reaction is very simple and clean because the by-products of the reaction are highly water soluble and can be easily removed by aqueous work-up. The structures of β-lactams **4a–p** were confirmed from spectroscopic data and elemental analyses. The *cis*/*trans* stereochemistry was assigned by the comparison of the H-3 and H-4 coupling constants ($J_{3,4}$ >4.0 Hz) for the *cis* stereoisomer and ($J_{3,4} \leqslant$ 3.0 Hz) for the *trans* stereoisomer.[8e]

This reaction is amenable for the gram scale synthesis. When *N*-(4-methoxybenzylidene)-4-methoxyaniline (3.0 g, 12.4 mmol) was treated with phenoxyacetic acid (2.8 g, 18.6 mmol), DMSO (1.3 mL, 18.6 mmol), Et_3N (8.6 mL, 62.0 mmol), and acetic anhydride (1.8 mL, 18.6 mmol) 2-azetidinone **4a** was obtained in 89% yield (4.1 g).

The synthesis of 2-azetidinone **4a** was also performed in the presence of other acid activators for comparison (Table 3). It is noteworthy that 2-azetidinone **4a** was obtained in high yield when activated DMSO or the Mukaiyama reagent was used as the acid activator at room temperature. The cost of the Mukaiyama reagent and its by-product are disadvantages of this reagent.

Table 2
Synthesis of 2-azetidinones **4a–p** using activated DMSO

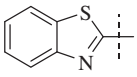
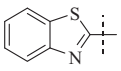
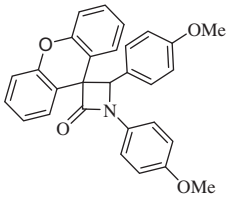
Entry	R^1	R^2	R^3	*cis*/*trans*	Product	Isolated yield (%)	mp (°C) (Lit.)
1	4-$MeOC_6H_4$	4-$MeOC_6H_4$	PhO	*cis*	**4a**	91	176–178 (177–178)[13j]
2	4-$MeOC_6H_4$	4-ClC_6H_4	PhO	*cis*	**4b**	93	180–182 (181–183)[13d]
3	4-MeONaphth-1-yl	4-$MeOC_6H_4$	PhO	*cis*	**4c**	91	169–171
4	4-MeONaphth-1-yl	4-ClC_6H_4	PhO	*cis*	**4d**	89	161–163
5		4-$MeOC_6H_4$	PhO	*cis*	**4e**	86	159–161
6	4-$MeOC_6H_4$	4-$MeOC_6H_4$	PhthN	*trans*	**4f**	88	196-198
7	4-$MeOC_6H_4$	4-ClC_6H_4	PhthN	*trans*	**4g**	84	225-227 (228-230)[13m]
8	4-MeONaphth-1-yl	4-ClC_6H_4	PhthN	*trans*	**4h**	85	180-182
9		4-$MeOC_6H_4$	PhthN	*trans*	**4i**	83	168-170
10	C_6H_5	4-$NO_2C_6H_4$	MeO	*cis*	**4j**	89	122–124 (124–126)[17c]
11	Me	4-$NO_2C_6H_4$	PhO	*cis*	**4k**	78	93-95 (91–93)[17c]
12	Me	$C_6H_5CH_2$	MeO	*cis*	**4l**	65	colorless oil
13	4-$MeOC_6H_4$	2-Furyl	PhO	*cis*	**4m**	87	151-153 (154-155)[13o]
14				–	**4n**	86	162-164 (161–163)[13d]

Table 2 (*continued*)

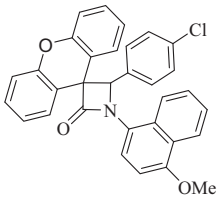
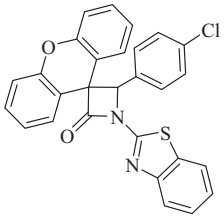
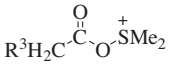
Entry	R^1	R^2	R^3	*cis*/*trans*	Product	Isolated yield (%)	mp (°C) (Lit.)
15				–	**4o**	82	157-159
16				–	**4p**	81	155-157

Table 3
Comparison of acid activators for the synthesis of 2-azetidinone **4a**

Entry	Acid activator	Temp	Yield (%)
1	DMSO/Ac_2O	rt	91
2	$POCl_3$	rt	62
3	Me_2S/Br_2	rt	67
4	Cyanuric chloride	rt	44
5	Cyanuric chloride	0 °C	71
6	Mukaiyama reagent	rt	83

Activated DMSO **1** can activate carboxylic acids to give an activated ester and then generate a ketene in situ in the presence of Et_3N. Finally, the ketene reacts with an imine to produce the β-lactam, according to the reported mechanism for the Staudinger synthesis.[17] Many different experimental factors, such as reaction temperature, solvent, electronic effects, and the steric hindrance of the ketene and imine substituents may affect the stereochemistry of β-lactams produced via the Staudinger synthesis. Phthalimidoketene has more steric hindrance than phenoxy- and methoxyketene, and gave rise to 3-phthalimido-2-azetidinones **4f–i** as *trans* isomers.



activated ester

In conclusion, a practical and efficient one-step synthesis of 2-azetidinones has been developed. The one-pot reaction of imines and substituted acetic acid with dimethyl sulfoxide and acetic anhydride [activated DMSO (**1**)] in the presence of triethylamine afforded 2-azetidinones in high yields. DMSO and Ac_2O are inexpensive and this reagent system is useful for both large and small scale reactions. This method is very convenient and the water-soluble by-products are removed by simple aqueous work-up.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.07.089.

References and notes

1. Li, W.; Liu, C.; Zhang, H.; Ye, K.; Zhang, G.; Zhang, W.; Duan, Z.; You, S.; Lei, A. *Angew. Chem., Int. Ed.* **2014**, *53*, 2443–2446.
2. Wang, F.-D.; Lin, M.-L.; Lee, W.-S.; Liu, C.-Y. *Int. J. Antimicrob. Agents* **2004**, *23*, 590–595.
3. Marumo, K.; Tekeda, A.; Nakamura, Y.; Nakaya, K. *J. Antimicrob. Chemother.* **1999**, *43*, 187–193.
4. (a) Arya, N.; Jagdale, A. Y.; Patil, T. A.; Yeramwar, S. S.; Holikatti, S. S.; Dwivedi, J.; Shishoo, C. J.; Jain, K. S. *Eur. J. Med. Chem.* **2014**, *74*, 619–656; (b) Mehta, P. D.; Sengar, N. P. S.; Pathak, A. K. *Eur. J. Med. Chem.* **2010**, *45*, 5541–5560; (c) Veinberg, G.; Vorona, M.; Shestakova, I.; Kanepe, I.; Lukevics, E. *Curr. Med. Chem.* **2003**, *10*, 1741–1757.
5. Xu, X.; Fu, R.; Chen, J.; Chen, S.; Bai, S. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 101–104.
6. For a review, see: (a) Alcaide, B.; Almendros, P.; Aragoncillo, C. *Chem. Rev.* **2007**, *107*, 4437–4492; (b) Alcaide, B.; Almendros, P. *Curr. Med. Chem.* **2004**, *11*, 1921–1949; (c) Deshmukh, A. R. A. S.; Bhawal, B. M.; Krishnaswamy, D.; Govande, V. V.; Shinkre, B. A.; Jayanthi, A. *Curr. Med. Chem.* **2004**, *11*, 1889–1920; (d) Ojima, I.; Delaloge, F. *Chem. Soc. Rev.* **1997**, *26*, 377–386; (e) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. *Synlett* **2001**, 1813–1826; (f) Palomo, C.; Oiarbide, M. In *Topics in Heterocyclic Chemistry*; Banik, B. K., Ed.; Springer: Berlin, 2010; Vol. 22, pp 211–259; (g) Alcaide, B.; Almendros, P. *Chem. Rec.* **2011**, *11*, 311–330.
7. (a) Hodge, M.; Chen, O.-H.; Bane, S.; Sharma, S.; Loew, M.; Banerjee, A.; Alcaraz, A. A.; Snyder, J. P.; Kingston, D. G. I. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2884–2887; (b) Suffness, M. *Taxol Science and Applications*; CRC Press: Boca Raton Florida, USA, 1995.
8. For a review, see: (a) Alcaide, B.; Almendros, P. *Prog. Heterocycl. Chem.* **2011**, *22*, 85–107; see also: (b) Aranda, M. T.; Perez-Faginas, P.; Gonzalez-Muniz, R. *Curr. Org. Synth.* **2009**, *6*, 325–341; (c) Fu, N.; Tidwell, T. T. *Tetrahedron* **2008**, *64*, 10465–10496; (d) Vankoten, D.; Van der Steen, F. H. *Tetrahedron* **1991**, *47*, 7503–7524; (e) Georg, G. I. *The Organic Chemistry of β-Lactams*; Verlag Chemie: New York, 1993; (f) Xu, J. *Tetrahedron* **2012**, *68*, 10696–10747; (g) Kamath, A.; Ojima, I. *Tetrahedron* **2012**, *68*, 10640–10664.
9. Staudinger, H. *Liebigs Ann. Chem.* **1907**, *356*, 51–123.
10. (a) Fodor, L.; Csomos, P.; Holczbauer, T.; Kalman, A.; Csampai, A.; Sohar, P. *Tetrahedron Lett.* **2011**, *52*, 224–227; (b) Zarei, M.; Karimi-Jaberi, Z.; Movahedi, A. *Synth. Commun.* **2013**, *43*, 728–734; (c) Keri, R. S.; Hosamani, K. M.; Shingalapur, R. V.; Reddy, H. R. S. *Eur. J. Med. Chem.* **2009**, *44*, 5123–5130; (d) Zarei, M.; Jarrahpour, A. *Synlett* **2011**, 2572–2576; (e) Zarei, M.; Mohamadzadeh, M. *Tetrahedron* **2011**, *67*, 5832–5840.
11. (a) Qi, H.; Yang, Z.; Xu, J. *Synthesis* **2011**, 723–730; (b) Tidwell, T. T. *Ketenes II*; John Wiley & Sons: New Jersey, 2006. pp 55–192.
12. (a) Kaminski, Z. J.; Kolesinska, B.; Kolesinska, J.; Sabatino, G.; Chelli, M.; Rovero, P.; Błaszczyk, M.; Głowka, M. L.; Papini, A. M. *J. Am. Chem. Soc.* **2005**, *127*, 16912–16920; (b) Unsworth, W. P.; Kitsiou, C.; Taylor, R. J. K. *Org. Lett.* **2013**, *15*, 258–261; (c) Unsworth, W. P.; Gallagher, K. A.; Jean, M.; Schmidt, J. P.; Diorazio, L. J.; Taylor, R. J. K. *Org. Lett.* **2013**, *15*, 262–265.
13. (a) Smith, S. R.; Douglas, J.; Prevet, H.; Shapland, P.; Slawin, A. M. Z.; Smith, A. D. *J. Org. Chem.* **2014**, *79*, 1626–1639; (b) Darvishi, A.; Zarei, M.; Akhgar, M. R. *Lett. Org. Chem.* **2013**, *10*, 645–650; (c) Jarrahpour, A.; Zarei, M. *Tetrahedron Lett.* **2009**, *50*, 1568–1570; (d) Jarrahpour, A.; Zarei, M. *Tetrahedron* **2009**, *65*, 2927–2934; (e) Nahmany, M.; Melman, A. *J. Org. Chem.* **2006**, *71*, 5804–5806; (f) Jarrahpour, A.; Zarei, M. *Molecules* **2007**, *12*, 2364–2379; (g) Bose, A. K.; Kapur, J. C.; Sharma, S. D.; Manhas, M. S. *Tetrahedron Lett.* **1973**, 2319–2320; (h) Jarrahpour, A.; Zarei, M. *Tetrahedron Lett.* **2007**, *48*, 8712–8714; (i) Zarei, M. *J. Chem. Res.* **2013**, *37*, 25–27; (j) Matsui, S.; Hashimoto, Y.; Saigo, K. *Synthesis* **1998**, 1161–1166; (k) Palomo, C.; Aizpurua, J. M.; Urchegui, R.; Iturburu, M.; de Retana, A. O.; Cuevas, C. *J. Org. Chem.* **1991**, *56*, 2244–2247; (l) Zarei, M.

Monatsh. Chem. **2013**, *144*, 1021–1025; (m) Zarei, M. *Tetrahedron* **2013**, *69*, 6620–6626; (n) Zigheimat, F.; Islami, M. R.; Nourmohammadian, F. *Synlett* **2014**, 229–232; (o) Arrieta, A.; Lecea, B.; Palomo, C. *J. Chem. Soc., Perkin Trans. 1* **1987**, 845–850.

14. Song, Y.; Shen, D.; Zhang, Q.; Chen, B.; Xu, G. *Tetrahedron Lett.* **2014**, *55*, 639–641.
15. (a) Albright, J. D.; Goldman, L. *J. Am. Chem. Soc.* **1967**, *89*, 2416–2423; (b) Katagiri, N.; Akatsuka, H.; Haneda, T.; Kaneko, C.; Sera, A. *J. Org. Chem.* **1988**, *53*, 5464–5470.
16. *General procedure:* Ac_2O (1.5 mmol) was added to a solution of substituted acetic acid (1.5 mmol), Schiff base (1.0 mmol), DMSO (1.5 mmol), and Et_3N (5.0 mmol) in dry CH_2Cl_2 (10 mL) at room temperature, and the mixture was stirred overnight. The mixture was washed successively with saturated $NaHCO_3$ (15 mL) and brine (15 mL). The organic layer was dried (Na_2SO_4), filtered and the solvent was removed under reduced pressure. The crude residue was purified by crystallization from EtOAc. 2-Azetidinone **4l** was purified by short column chromatography (hexane/EtOAc 8:2). *1-(Benzo[d]thiazol-2-yl)-4-(4-methoxyphenyl)-3-phenoxy-azetidin-2-one* (**4e**): Light-yellow solid. mp 159–161 °C IR (KBr) cm^{-1}: 1636 (C=N), 1751 (CO, β-lactam); ^1H NMR (250 MHz, $CDCl_3$) δ 3.68 (OMe, s, 3H), 4.59 (H-4, d, 1H, J = 4.8), 5.45 (H-3, d, 1H, J = 4.8), 6.88-7.97 (ArH, m, 13H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 55.5 (OMe), 62.0 (C-3), 81.6 (C-4), 111.9, 121.7, 123.5, 123.9, 124.3, 126.8, 127.5, 129.0, 129.4, 129.6, 132.7, 141.4, 149.1, 152.4 (aromatic carbons), 161.7 (C=N), 163.3 (CO, β-lactam); Anal. Calcd for $C_{23}H_{18}N_2O_3S$: C, 68.64; H, 4.51; N, 6.96. Found: C, 68.71; H, 4.64; N, 7.02.
17. (a) Wang, Y.; Liang, Y.; Jiao, L.; Du, D.-M.; Xu, J. *J. Org. Chem.* **2006**, *71*, 6983–6990; (b) Jarrahpour, A.; Zarei, M. *Tetrahedron* **2010**, *66*, 5017–5023; (c) Zarei, M. *Bull. Chem. Soc. Jpn.* **2012**, *85*, 360–368; (d) Manhas, M. S.; Amin, S. G.; Glazer, R. D. *Synthesis* **1979**, 210–213.

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