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Silphos as an efficient heterogeneous reagent for the synthesis of 2-azetidinones

Abstract: This report provides a description of an efficient and simple procedure for the synthesis of 2-azetidinones *via* a one-pot reaction of imines and carboxylic acids in the presence of silicaphosphine at room temperature. The reagent is cheap and stable. The yields are good to excellent, and the reaction conditions are mild.

Keywords: 2-azetidinone; β-lactam; ketene; Schiff base; silphos; Staudinger reaction.

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Introduction

β-Lactam antibiotics, such as penicillins, cephalosporins, carbapenems, and aztreonam, serve as effective agents against bacterial infections [1–3]. Their activity is due to the presence of a 2-azetidinone ring [4]. Some monocyclic β-lactam (2-azetidinone) derivatives possess a wide variety of pharmacological activities [5–7]. For example, ezetimibe is used clinically for its cholesterol absorption inhibitory property [8, 9]. Use of 2-azetidinones in the synthesis of many classes of compounds is well established [10–13] including the semi-synthesis of taxol derivatives [14].

β-Lactam ring formation is a crucial step in the synthesis of new β-lactams. As such, new synthetic methods for the preparation of the β-lactam ring have been developed [15–20]. The Staudinger reaction [21] (ketene-imine cycloaddition) is undoubtedly the most widely used route to 2-azetidinones [22–28]. Ketenes are commonly generated by reaction of acyl halides with tertiary amines [29–31], however, the use of acyl halides generally is not an easy or safe task. The preparation of ketenes from carboxylic acids is a more practical process [32–46]. A common approach to the synthesis of β-lactams involves treatment of the acid with activators (i.e., triphenylphosphine dibromide [47], $POCl_3$ [48], and some other phosphorus reagents [49–52]) to form an activated intermediate, which can be treated with a base to form a ketene *in situ* [32–46]. However, in addition to tedious reaction conditions, some acid activators are quite expensive, and separation of the byproducts is difficult. Especially difficult is the removal of phosphine oxide derivatives, which is a disadvantage in the use of phosphorus reagents in the aforementioned reactions. To this end, we realized that use of supported reagents may offer practical advantages [53].

Silicaphosphine (silphos), $[P(Cl)_{3-n}(SiO_2)_n]$, is easily prepared by the reaction of silica gel and PCl_3 [54]. Silphos has been applied for the conversion of alcohols and thiols to alkyl bromides and iodides [54], acetylation and formylation of alcohols and amines with ethyl formate and acetate [55], deoxygenation of sulfoxides to thioethers, reductive coupling of sulfonyl chlorides, conversion of sodium sulfinates and thiosulfonates to their corresponding disulfides [56], regioselective synthesis of *vic*-haloalcohols [57], conversion of oximes to nitriles and amides or carbonyl compounds [58], as well as the Beckmann rearrangement of ketoximes and dehydration of aldoximes [59]. To our best knowledge, there are no reports on the use of silphos in β-lactam ring formation. Herein, we report the practical application of this heterogeneous reagent in the synthesis of 2-azetidinones.

Results and discussion

The reaction of phenoxyacetic acid and *N*-(4-chlorobenzylidene)-4-ethoxyaniline with PCl_3 in the presence of triethylamine in dry dichloromethane at room temperature did not afford a β-lactam product. When the reaction was performed at low temperature (-12°C), the desired 2-azetidinone **3a** was formed in a 6% yield.

Then it was decided to attempt to generate the β-lactam ring in the presence of Silphos [54–59]. Silphos was prepared as a white solid as described [54]. The reaction of phenoxyacetic acid and *N*-(4-chlorobenzylidene)-4-ethoxyaniline in dry dichloromethane at room temperature in the presence

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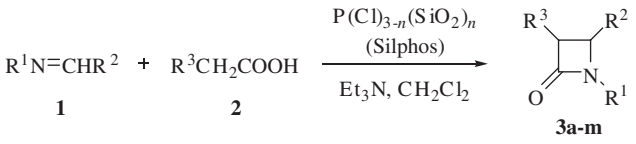
Table 1 Reaction condition in the synthesis of **3a**.

Entry	Solvent	Temp (°C)	Reagent (mmol)	Yield (%)
1	CH_2Cl_2	rt	PCl_3 (1.0)	–
2	CH_2Cl_2	-12	PCl_3 (1.0)	6
3	CH_2Cl_2	rt	Silphos (1.0)	57
4	Toluene	rt	Silphos (1.0)	43
5	DMF	rt	Silphos (1.0)	25
6	CH_2Cl_2	0	Silphos (1.0)	55
7	CH_2Cl_2	rt	Silphos (1.2)	83
8	CH_2Cl_2	rt	Silphos (1.3)	88
9	CH_2Cl_2	rt	Silphos (1.5)	87

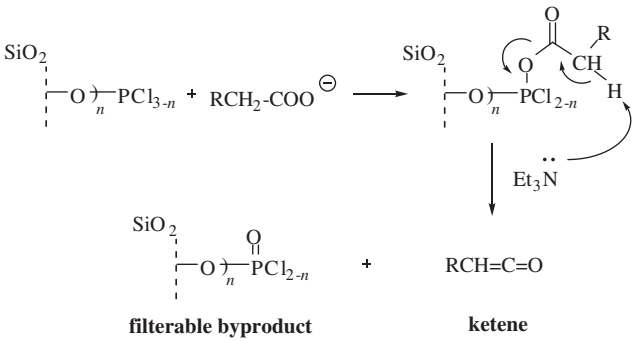


Scheme 1

of triethylamine and silphos afforded 2-azetidinone **3a** in 57% yield after crystallization from EtOAc (Table 1, entry 3).

Based on this successful result, we tried to optimize the effects of different solvents, temperatures, and the amounts of silphos. As shown in Table 1, dry dichloromethane is the best solvent for this reaction. The highest yield of **3a** is obtained when 1.0 mmol of Schiff base undergoes a reaction with 1.3 mmol of phenoxyacetic acid in the presence of 1.3 mmol of silphos in dry dichloromethane at room temperature (Table 1, entry 8).

The generality of this strategy is shown in Scheme 1 and Table 2. The synthesis was extended to several types



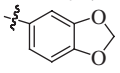
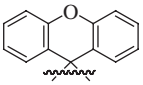
Scheme 2

of monocyclic β-lactams bearing diverse substituents. β-Lactams **3a**–**g** and **3k–m** were purified by recrystallization from EtOAc and β-lactams **3h–j** were purified by short-column chromatography on silica gel (hexane/EtOAc=9:1).

The structure of new product **3b** was confirmed by ^{1}H NMR, ^{13}C NMR, IR, and elemental analysis. The ^{1}H NMR spectrum of **3b** shows the characteristic AB pattern of the β-lactam ring protons H-4 at δ 4.7 and δ 5.3 of the proton H-3. The coupling constant of 4.5 Hz indicates *cis* stereochemistry. In general, the coupling constant smaller than 3 Hz is indicative of *trans* stereochemistry. The remaining products have been described previously, and their spectral data are virtually identical with those reported.

According to the accepted mechanism of the Staudinger reaction [60–62], it is suggested that the reaction involves the formation of an activated ester (Scheme 2) and a ketene. Then the intermediate ketene undergoes a reaction with an imine to produce the β-lactam [60–62].

Table 2 Synthesis of 2-azetidinones **3a–m** using Silphos.

Entry	R^1	R^2	R^3	*cis*/*trans*	Product
1	4-$EtOC_6H_4$	4-ClC_6H_4	PhO	*cis*	**3a**
2		4-$MeOC_6H_4$	PhO	*cis*	**3b**
3	Ph	4-$NO_2C_6H_4$	MeO	*cis*	**3c**
4	4-$MeOC_6H_4$	4-$NO_2C_6H_4$	2,4-$Cl_2C_6H_3O$	*cis*	**3d**
5	4-EtC_6H_4	4-$(Me_2N)C_6H_4$	4-ClC_6H_4O	*cis*	**3e**
6	Ph	4-$NO_2C_6H_4$	2-NaphthO	*cis*	**3f**
7	4-$EtOC_6H_4$	4-$MeOC_6H_4$	PhthN	*trans*	**3g**
8	4-$MeOC_6H_4$	4-ClC_6H_4		*trans*	**3h**
9	4-$EtOC_6H_4$	C_6H_5	N_3	*cis*	**3i**
10	Ph	4-ClC_6H_4	4-$MeC_6H_4SO_2$	*trans*	**3j**
11	Bn	4-ClC_6H_4	PhO	*cis*	**3k**
12	4-$MeOC_6H_4CH_2$	4-$NO_2C_6H_4$	2,4-$Cl_2C_6H_3O$	*cis*	**3l**
13	Ph	4-ClC_6H_4		–	**3m**

Experimental

General

IR spectra were run on a Shimadzu FT-IR 8300 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ using a Bruker Avance DPX instrument. Elemental analyses were run on a Thermo Finnigan Flash EA-1112 series instrument. Melting points were determined in open capillaries with Buchi 510 melting point apparatus. Thin-layer chromatography was carried out on silica gel 254 analytical sheets obtained from Fluka. Column chromatography was performed on Merck Kiesel gel (230–270 mesh).

General procedure for synthesis of 2-azetidinones 3a–m

To a solution of an imine (1.0 mmol), carboxylic acid (1.3 mmol), and dry Et_3N (5.0 mmol) in dry CH_2Cl_2 (10 mL) was added silphos (1.0 g, 1.3 mmol) at room temperature, and the resulting mixture was stirred overnight. Then the mixture was filtered and the filtrate was washed successively with saturated $NaHCO_3$ (10 mL) and brine (10 mL). The organic layer was dried (Na_2SO_4) and filtered, and the solvent was removed to give the crude product. β-Lactams **3a–g** and **3k–m** were purified by crystallization from EtOAc and β-lactams **3h–j** were purified by short-column chromatography on silica gel (hexane/EtOAc, 9:1).

4-(4-Chlorophenyl)-1-(4-ethoxyphenyl)-3-phenoxyazetidin-2-one (3a) [37]: Yield 88%.

1-(Benzo[*d*][1,3]dioxol-5-yl)-4-(4-methoxyphenyl)-3-phenoxyazetidin-2-one (3b): Yield 90%; mp 159–161°C; IR (KBr): 1749 cm^{-1} (CO, β-lactam); ^{1}H NMR: δ 3.78 (OMe, s, 3H), 5.11 (H-4, d, 1H, J = 4.5 Hz), 5.37 (H-3, d, 1H, J = 4.5 Hz), 5.85 (OCH_2O, s, 2H), 6.77–7.82 (ArH, m, 12H); ^{13}C NMR: δ 56.0 (OMe), 61.8 (C-4), 82.4 (C-3), 111.6 (OCH_2O), 108.6, 113.1, 119.1, 122.0, 122.9, 125.7, 128.3, 129.5, 130.2, 131.8, 134.1, 142.6, 149.4, 158.1 (aromatic carbons), 162.9 (CO, β-lactam). Anal. Calcd for $C_{23}H_{19}NO_5$: C, 70.94; H, 4.92; N, 3.60. Found: C, 71.05; H, 5.04; N, 3.54.

3-Methoxy-4-(4-nitrophenyl)-1-phenylazetidin-2-one (3c) [62]: Yield 85%.

3-(2,4-Dichlorophenoxy)-1-(4-methoxyphenyl)-4-(4-nitrophenyl)-azetidin-2-one (3d) [61]: Yield 91%.

3-(4-Chlorophenoxy)-4-(4-(dimethylamino)phenyl)-1-(4-ethylphenyl)azetidin-2-one (3e) [16]: Yield 91%.

3-(Naphthalen-2-yloxy)-4-(4-nitrophenyl)-1-phenylazetidin-2-one (3f) [33]: Yield 93%.

2-(1-(4-Ethoxyphenyl)-2-(4-methoxyphenyl)-4-oxoazetidin-3-yl) isoindoline-1,3-dione (3g) [35]: Yield 83%.

4-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-vinylazetidin-2-one (3h) [35]: Yield 67%. yield.

3-Azido-1-(4-ethoxyphenyl)-4-phenylazetidin-2-one (3i) [38]: Yield 59%.

4-(4-Chlorophenyl)-1-phenyl-3-tosylazetidin-2-one (3j) [33]: Yield 52%.

1-Benzyl-4-(4-chlorophenyl)-3-phenoxyazetidin-2-one (3k) [61]: Yield 89%.

3-(2,4-Dichlorophenoxy)-1-(4-methoxybenzyl)-4-(4-nitrophenyl)-azetidin-2-one (3l) [40]: Yield 92%.

2-(4-Chlorophenyl)-1-phenylspiro[azetidine-3,9′-xanthen]-4-one (3m) [33]: Yield 83%.

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