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Microwave-Assisted Solvent-Free Organic Reactions: Synthesis of β-Lactams from 1,3-Azadienes

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Abstract

Ring-closure of 1,3-azadienes to β-lactam rings is efficiently and quickly carried out under solvent-free conditions in an open-vessel microwave system. The synthesis of *N-tert*-butyldimethylsilyl azetidinones is reported.

Keywords: Microwave heating, Azetidinones, Staudinger, Cyclization.

During recent years numerous studies have been reported on the venerable Staudinger reaction [1] for the preparation of azetidinones which are valuable building blocks in the construction of synthetic β-lactam antibiotics [2] . Recently Bose reported the utilisation of a microwave-technique (the MORE technique) for the production of such derivatives [3,4] .

The first examples of the rapid synthesis of organic compounds using microwave ovens were reported by Gedye [5]. Since then a number of papers have appeared concerning microwave-assisted organic reactions and the number of articles continues to grow quickly [6-8] . The main advantages of microwave-assisted organic synthesis are shorter reaction times, minimum waste and generally higher yields. A particularly attractive feature of the microwave technique is the possibility of carrying out reactions in the absence of solvent since "*The day may be coming when drastic restrictions on solvent pollution will require the adoption of no-solvent reactions*" [6] . Following our recent work on the synthesis of azetidin-2-ones through a two-step Staudinger reaction, we began a systematic study to address the use of microwave techniques in the synthesis of β-lactam rings from 1,3-azadienes in the absence of solvents. We wish to report here our preliminary results on a practical and simple technique using a normal domestic microwave oven, without alteration, as a safe and convenient laboratory device. As will be seen from the subsequent discussion, the cyclization can be conducted on a scale from milligrams to fifty grams in 1-20 min using inexpensive equipment. Furthermore, there is no need for sealed vessels, reflux condensers, stirrers or an inert-gas atmosphere. The key to our solvent free organic reactions is the proper choice of irradiation time and control of the energy input from the microwave oven into the reaction mixture. In this way, the reaction temperature is kept below a critical value which may be responsible for the decomposition of the starting azadiene and/or the target compound. Since it is not easy to predict this value, which depends on the nature of the substrate and the quantity of starting material, a set of experiments were performed to find out the best

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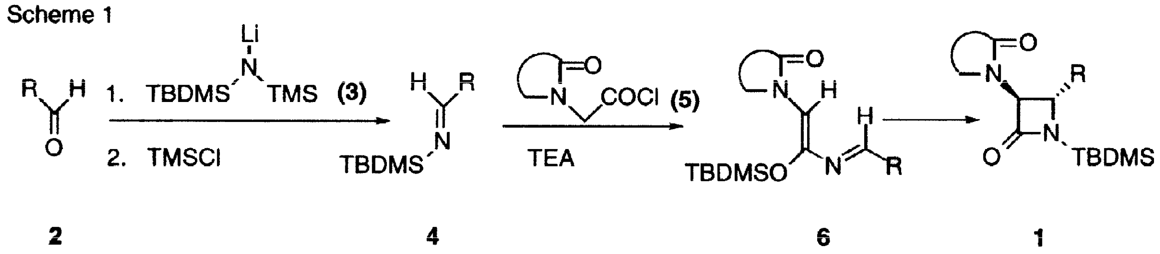
conditions for obtaining high cyclization yield. The starting azadiene was generated from a silylimine, which was in turn prepared from an aldehyde and an acyl chloride [9-11] . In order to have stable azadienes and already protected *N*-azetidinones, we have prepared the *N*-trialkylsilyl-substituted azadienes **6** with the hydrolytically stable TBDMS-group. The required *N*-*tert*-butyldimethylsilyl imine **4** was prepared from lithium *N,N*-(*tert*-butyldimethyl)trimethylsilyl amide **3** and an aldehyde **2** according to the reported procedures (Scheme 1) [12,13] .

Scheme 1



Azadienes **6** thus prepared are reasonably stable and were used as such or purified by flash chromatography on a short silica gel-column depending on the purity of the crude reaction mixture as evaluated by ^{1}H NMR (Yields of isolated azadienes are reported in square brackets in Table 1). Azadienes derived from *tert*-butyldimethylsilylimines may be stored at -18°C without appreciable decomposition[&] [14]. Irradiation of azadiene **6** in an open-vessel microwave system, for the amount of time and with the energy reported in Table 1, gave the azetidinones **1** in satisfactory to good yields. The reaction has been scaled-up to 100 mmol scale without appreciable variations in the yields and diastereomeric ratio. It must be pointed out that, even with this new method of cyclization, *the simple diastereoselectivity is invariably trans* while the facial diastereoselectivity resembles that obtained upon refluxing the azadiene in toluene. This shows the independence of the diastereomeric ratio from the solvent.

Procedure for the synthesis of azetidinone **6a** *on 100 mmol scale.*

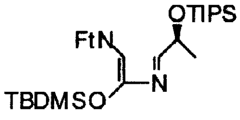
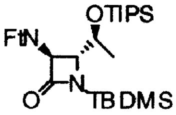
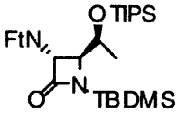
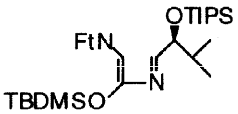
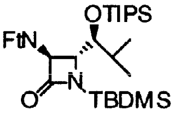
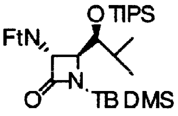
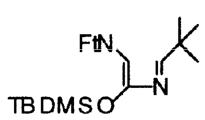
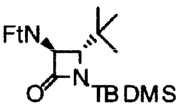
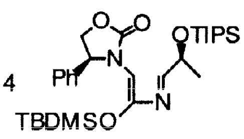
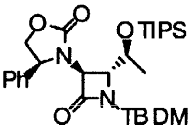
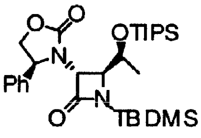
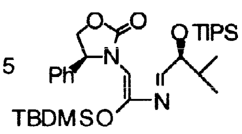
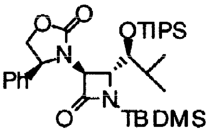
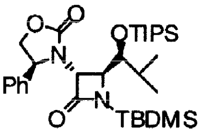
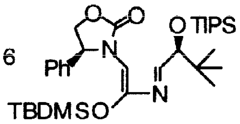
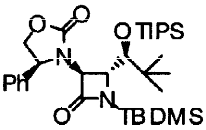
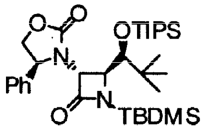
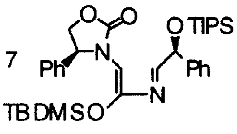
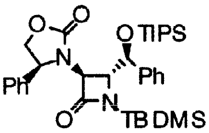
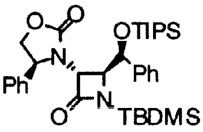
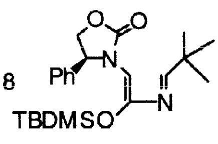
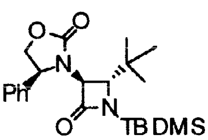
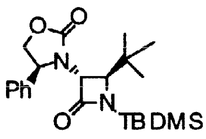
To a solution of *N,N*-(*tert*-butyldimethylsilyl)trimethylsilylamine (20.2 g, 100 mmol) in heptane (80 ml) was added butyllithium (100 mmol, 40 ml of a 2.5 M solution in hexane) at 0°C; *O*-triisopropylsilyllactaldehyde **2a** (23.0 g, 100 mmol) in heptane (20 ml) was added after 30 min., to the lithium *N,N*-(*tert*-butyldimethylsilyl)trimethylsilylamide **3** at -10°C. The reaction mixture was stirred for 30 min. and TMSCl (13 ml, 100 mmol) was added in one portion at 0°C. Stirring was continued at r.t. for 1h. after which time the reaction mixture was cooled to 0°C and TEA (27.8 ml, 200 mmol) was added. The phthaloylglycyl chloride **5a** (22.3 g, 100 mmol) in toluene (80 ml) was added dropwise. Stirring was maintained for 1.5 h. during which time a large amount of precipitate appeared. The precipitate was filtered through diatomaceous earth and the solvent removed *in vacuo*. The crude azadiene **6a** [15] thus obtained was purified by flash-chromatography on a short silica gel column eluting with hexane-ethyl acetate 80/20 (45 g, 85% yield).

Solvent Free Microwave Organic Reaction.

The azadiene, prepared according the procedure reported above, was placed in an Erlenmeyer flask and irradiated for 3min[$] at 650 W to give the azetidinone **1a** (32.4 g, 72%).

[&] In contrast azadienes prepared from trimethylsilylimines gave rise, on standing, to the corresponding azetidinone.

Table 1: Synthesis of Azetidinones 1

Entry[a]	Azadiene	β-Lactams[b]		Time (min)	Energy (Watt)	Yield[c]	Ratio[d] 1/*d*-1	Ref
1	 **6** [Y%=85]	 **1a**	 ***d*-1a**	3	660	72	50/50	9
2	 **7** [Y%=32]	 **1b**	 ***d*-1b**	20	660	61	85/15	9
3	 **8** [Y%=54]	 ***rac*-1c**		20	660	44		9
4	 **9** [Y%=54]	 **1d**	 ***d*-1d**	20	660	81	60/40	10
5	 **10** [Y%=50]	 **1e**	 ***d*-1e**	20	660	57	90/10	10
6	 **11** [Y%=68]	 **1f**	 ***d*-1f**	20	660	67	56/44	10
7	 **12** [Y%=25	 **1g**	 ***d*-1g**	20	660	90	80/20	10
8	 **13** [Y%=50]	 **1h**	 ***d*-1h**	20	660	60	63/37	10

a: The reactions were performed, except for entry 1, on a 2 mmol scale.

b: A certain amount (5-10%) of the unprotected *N*-azetidinone may be present in the crude mixture.

c: Diastereomeric ratios were determined by ^{1}H NMR of the crude reaction mixture.

d: Yields of pure isolated products. All the products gave satisfactory IR, ^{1}H NMR, ^{13}C NMR and MS analysis.

Table 1 reports the results obtained in the synthesis of azetidinones from azadienes using the procedure described above. Entries 2-8 were performed on a two mmol scale with irradiation for 20min.

From the results reported in Table 1 it is evident that this method of cyclization, based on microwave-assisted solvent-free organic reactions, is very efficient. Yields are at least equivalent, or even slightly better than those described in the literature and experimental conditions are exceptionally mild. The procedure avoids solvents and reactions are complete in a very short time under safe conditions. Finally the possibility of isolating the final product as its *N*-TBDMS derivative confers to our system an extra advantage. Extension of this work to more challenging cases is currently in progress in our laboratories.

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