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A Greener Technique for Microwave-Assisted O-Silylation and Silyl Ether Deprotection of Uridine and Other Substrates

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Abstract: A single clean, good-yielding, environment-friendly microwave-assisted procedure for *O*-silylation of uridine with *tert*-butyldimethylsilyl chloride (TBDMSCl), 1,8-Diazabicyclo(5.4.0)undec-7-ene (DBU) and potassium nitrate as catalyst under solvent-free conditions is reported. Subsequent silyl ether deprotection is accomplished with a reusable acidic resin via microwave irradiation. Both the silylation and desilylation protocols have been applied to a panel of alcohols of pharmaceutical interest.

Keywords: silylation; solvent-free; microwave; resin cleavage

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1. Introduction

The hydroxyl functional group can be found almost ubiquitously in compounds of pharmaceutical interest, such as nucleosides, carbohydrates, terpenes and steroids [1].

Silyl ethers are among the most frequently used protective groups for alcohols thanks to the variability of both their steric properties and cleavage conditions [2–4]. Important applications are described in the field of antiviral research, for the synthesis of nucleoside analogues [5,6]. Among them, molnupiravir has recently attracted interest due to its broad-spectrum antiviral activity, in particular against the SARS-CoV-2 virus. Corey-Venkateswarlu [7] described the use of a silyl chloride with imidazole in N,N′-dimethylformamide (DMF) to promote O-silylation of primary and secondary alcohols, and since then, many other silylation procedures with different silylating agents, bases and other additives have been developed [2–4,8,9]. However, despite being trustworthy and useful synthetic allies, the use of protecting groups often struggles to meet with green and clean chemistry principles [10]. In fact, among the bases and catalysts adopted, efficient results have been reported with pyridine or pyridine derivatives such as pyridine N-oxide, and 4-dimethylaminopyridine, iodine and lithium sulfide, known for their relevant toxicity for operators and the environment [3,11]. Thus, the development of safer and environmentally friendly procedures for both the introduction and cleavage of protecting groups is of considerable interest [12–14]. Many efforts have been recently made to limit the use of toxic and pollutant systems, including their replacement with safer chemicals or the use of less-impacting technologies. Solvent-free and microwave-assisted reactions are receiving increasing attention from the viewpoint of green and clean chemistry [15]. Recently, during our studies on the development of a cleaner uridine O-silylation protocol, we found that microwave irradiation made the reaction considerably fast and good-yielding. We report herein a new solvent-free microwave-assisted O-silylation procedure for uridine and other alcohols and a microwave-assisted cleavage of the obtained silyl ethers with a reusable acidic resin.

2. Materials and Methods

2.1. Materials and Instruments

All commercially available reagents and solvents were used as purchased without further purification (Sigma-Aldrich, St Louis, MO, USA), (Alfa-Aesar, Kandel, Germany) (Carlo Erba, Rodano, Milano, Italy). Dry DMF was used as purchased and dichloromethane (DCM) was distilled from CaH_2 directly before use.

Microwave-assisted reactions were performed in a single mode using a CEM Discover Synthesis Unit (CEM Corp., Matthews, NC, USA)^{TM} microwave. A continuous microwave power ranging from 0 to 300 W has been applied. A calibrated infrared temperature control was used to measure the temperature of the vessel. The method used for all experiments involved stirring the reaction mixture with a Teflon-coated magnetic stir bar inside the vessel.

Progress of the reaction was monitored by thin-layer chromatography (TLC) using Merck TLC silica gel 60 F_{254} using the appropriate eluent as described in the Supplementary Materials. Column chromatography was performed on Merck 60 Å silica gel, 230–400 mesh, for flash technique.

^{1}H and ^{13}C spectra were recorded at 400 MHz on a Bruker UltraShield^{TM} 400 instrument (400 MHz for ^{1}H and 101 MHz for ^{13}C NMR spectroscopy), or a 600 MHz on a Bruker UltraShield^{TM} 600 instrument (600 MHz for ^{1}H and 242 MHz for ^{13}C NMR spectroscopy). Chemical shifts are reported in parts per million (δ scale), relative to TMS peak.

Mass spectra (LC-MS) were acquired using an Agilent 1100 LC-MSD VL system (G1946C) with an electrospray ionization source (ESI). Data were obtained by direct injection with a 0.4 mL/min flow rate using a binary solvent system of 95/5 (v/v) methanol (MeOH)/H_2O. Mass spectra were acquired in positive- or negative-mode scanning over the mass range 105–1500 m/z, using a variable fragmentor voltage of 10–70 mV (0–70).

The purity of final products was assessed by HPLC-MS and was above 90%.

2.2. General Procedure for the Synthesis of Silyl Ethers

The appropriate alcohol (1.0 mmol), KNO_3 (0.3 mmol) and 1,8-Diazabicyclo(5.4.0)undec-7-ene (DBU) (2.7 mmol) were added to a microwave tube equipped with a magnetic stirrer. Then, *tert*-butyldimethylsilyl chloride (TBDMS-Cl) (1.5 mmol) was added to the mixture, the tube capped and the reaction was stirred in the microwave at 75 °C, 300 W, 100 PSI, on high-stirring mode and with the cooling option on. For entry **10**, due to the volatility of both the starting alcohol and silyl ether obtained, the temperature was lowered to 60 °C. The completion of the reaction was monitored via TLC. The reaction mixture was washed with water and extracted with ethyl acetate (AcOEt) (3 × 25 mL). In the case of **1**, the reaction mixture was treated with triethylamine phosphate buffer 0.5 M (pH = 7) and extracted with AcOEt (3 × 25 mL). The combined organic layers were washed with brine (saturated solution), dried on anhydrous Na_2SO_4 and evaporated under reduced pressure. The products were purified by silica gel flash column chromatography (petroleum ether (PE)/AcOEt 9:1 for entries **1** and **8**; PE/AcOEt 95:5 for entries **2**, **4**, **5**, **6**, **7**; PE/AcOEt 99:1 for entry **3**, PE/AcOEt 98:2 for entry **9**, PE/Et_2O 98:2 for entry **10**). The purified compounds were characterized by ^{1}H and ^{13}C NMR analysis and HPLC-MS (for details, see Supplementary Materials). *Note*: When performing scaling-up of the reaction conditions up to 1 g of starting uridine, the addition of the reagents was performed at 0 °C (exothermic reaction) and the microwave cooling function was turned on to prevent overheating.

2.3. General Procedure for the Synthesis of Alcohols via Deprotection of Silyl Ethers

The appropriate silyl ether (1.0 mmol), Dowex 50WX4-200 (2:1 w/w) and MeOH (0.5 mL) were added to a microwave tube without a magnetic stirrer. The mixture was allowed to incubate at rt in a vortex stirrer for 30–60 min at 160–200 rpm. Then, the reaction mixture was stirred in the microwave at 50–60 °C, 300 W and 100 PSI. The completion of the reaction was monitored via TLC. The reaction mixture was filtered with a vacuum-connected gooch funnel, and the Dowex beads were washed several times with MeOH.

Then, the solvent was evaporated under reduced pressure. For derivative **D4**, additional work-up was performed, by treating with water and extracting with AcOEt (3 × 25 mL). The combined organic layers were washed with brine (saturated solution), dried on anhydrous Na_2SO_4 and evaporated under reduced pressure. The products were purified by silica gel flash column chromatography (DCM/MeOH 95:5→ 9:1 for entry **D1**, PE/AcOEt 99:1→ 95:5 for entry **D2**; PE/AcOEt 95:5 for entry **D4**). Entry **D3** was characterized without further purification. The desired product in entry D5 has not been obtained. The purified compounds were characterized by ^{1}H and ^{13}C NMR analysis, and HPLC-MS (for details, see Supplementary Materials).

3. Results and Discussion

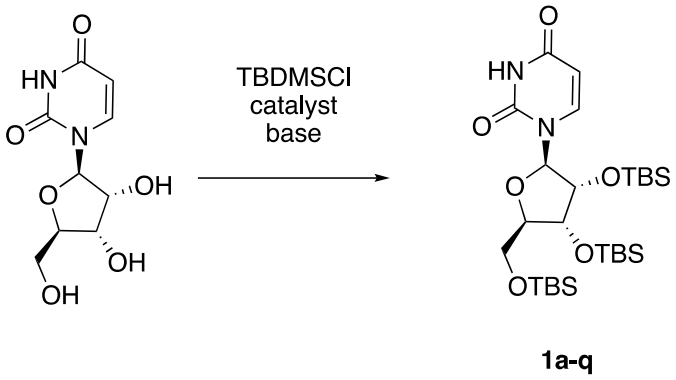
3.1. O-Silylation of Uridine

Preliminary experiments on *O*-silylation of uridine with TBDMSCl with different bases and additives (Scheme 1) were carried out in order to increase yields, reduce reaction times and find more sustainable reaction conditions. The adopted conditions and results are shown in Table 1 (entries **1a**–**q**).

Table 1. *O*-silylation of uridine with TBDMSCl using different catalysts, solvent bases and reaction setup.

Entry	TBDMSCl (mmol)	Catalyst (mmol)	Base/Nucleophile (mmol)	Solvent	Heating Method	Time	Yield
1a	4.0	DMAP (0.1)	Imidazole (4.0)	DCM	None	3 d	11%
1b	6.0	/	Imidazole (10.0)	DMF	Conventional	48 h	27%
1c	12.0	$AgNO_3$ (11.0)	Imidazole (26.0)	DMF	Conventional	3 h	86%
1d	12.0	KNO_3 (11.0)	Imidazole (26.0)	DMF	Conventional	3 h	97%
1e	12.0	KNO_3 (11.0)	Imidazole (26.0)	DMF	None	3 h	47%
1f	12.0	KNO_3 (11.0)	Imidazole (26.0)	DMF	MW	5 min	99%
1g	12.0	KNO_3 (11.0)	$CsCO_3$ (26.0)	DMF	MW	5 min	/
1h	12.0	KNO_3 (11.0)	Na_2CO_3 (26.0)	DMF	MW	5 min	/
1i	12.0	KNO_3 (11.0)	Imidazole (26.0)	2-Me-THF	MW	5 min	99%
1j	6.0	KNO_3 (6.0)	Imidazole (26.0)	2-Me-THF	MW	10 min	19%
1k	9.0	KNO_3 (8.2)	Imidazole (19.5)	2-Me-THF	MW	50 min	88%
1l	9.0	KNO_3 (8.2)	DBU (19.5)	2-Me-THF	MW	5 min	90%
1m	9.0	KNO_3 (3.0)	DBU (19.5)	2-Me-THF	MW	10 min	89%
1n	9.0	KNO_3 (1.0)	DBU (19.5)	2-Me-THF	MW	10 min	99%
1o	6.0	KNO_3 (1.0)	DBU (13.0)	2-Me-THF	MW	10 min	90%
1p	6.0	KNO_3 (1.0)	2,6-lutidine (13.0)	2-Me-THF	MW	10 min	21%
1q	4.5	KNO_3 (1.0)	DBU (8.0)	Solvent-free	MW	10 min	98%

Reaction conditions: All reactions were carried out at 75 °C unless otherwise stated. 2-Me-THF = 2-methyltetrahydrofuran; MW = Microwave.



Scheme 1. *O*-silylation of uridine.

The initial reaction system was composed by uridine, with TBDMSCl as the silylating agent, imidazole as the base and DCM or DMF as the solvent. Entries **1a** and **1b** were performed according to literature procedures [16,17], but very low yields, long reaction times and a mixture of disilylated and trisilylated compounds were observed.

The use of catalysts such as iodine or $AgNO_3$ in silylation reactions has already been described in literature [2,11,18]. According to these studies, the addition of $AgNO_3$ to the reagent system (entry **1c**) considerably enhanced the yield and reduced the reaction time. In order to evaluate the role of the nitrate ion and its counterion on the reaction outcome, the experiment was conducted with KNO_3 with excellent yield (97%, entry **1d**). Due to concerns related to the use of silver [19,20], and the lower cost, KNO_3 was chosen in place of $AgNO_3$ for the rest of the experiments as a cheap and safer alternative.

Temperature control proved to be necessary for the silylation to proceed; lower temperatures are detrimental to the yield, reducing the yield from 97 to 47% (entry **1d** and **1e**, respectively).

Microwave irradiation gave excellent results (entry **1f**) in terms of yield, reaction times and selectivity, yielding only the trisilylated uridine derivative, and was thus chosen as the heating method for the rest of the study.

After optimizing the heating method and catalyst, we replaced DMF with the cleaner 2-methyl tetrahydrofuran [21,22] (entries **1i**–**1p**), a non-toxic and sustainable solvent obtained from various lignocellulosic feedstocks. Then, we focused our attention on greener alternatives to imidazole. The best results were obtained with 1,8-diazabicyclo[5.4.0]undec-7-ene [23–25] (DBU), already included in the GSK-suggested environmentally friendly list of bases (**1n**–**1o**) [26]. On the contrary, inorganic bases and other green organic alternatives such as 2,6 lutidine gave poor results (**1g**–**1h**, **1p**) [2]. To improve the atom economy of the reaction and avoid unnecessary stochiometric excess of reagents used, various attempts were made, reducing the quantity of potassium nitrate, silylating agent and base (**1m**–**1o**, **1q**). As shown in entry **1n**–**1o**, KNO_3 can be considered catalytic for the reaction.

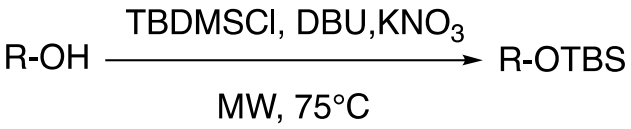
Finally, the reaction was performed in solvent-free conditions [27] (entry **1q**), reducing TBDMSCl and DBU to 1.5 eq and 2.7 eq, respectively. Excellent yields were obtained, optimizing the protocol in terms of yield, reaction time and greenness. Differently from the procedures already described [16], we obtained the target triprotected uridine **1** without using toxic reagents, harmful solvents [2] and with significantly reduced reaction time (10 min vs. 18 h). Most importantly, the setup is extremely simple, and the reaction was performed in the presence of air and without the need of anhydrous solvents, as reported in classic procedures.

The reaction was satisfactorily applied on a medium scale (200 mg of starting uridine), obtaining a comparable yield and reaction time.

3.2. Scope Variation

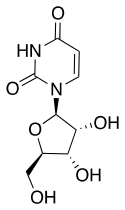
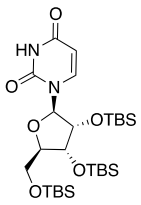
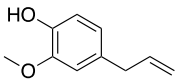
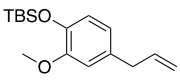
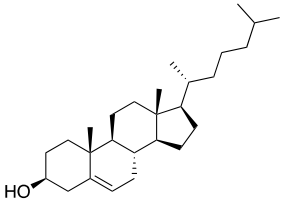
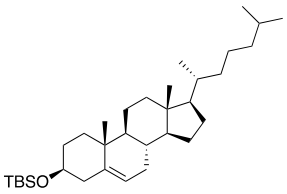
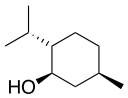
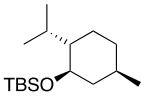
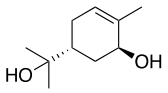
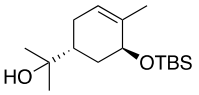
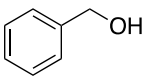
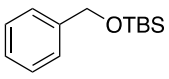
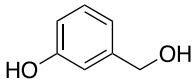
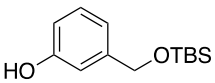
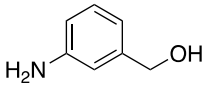
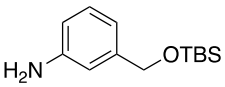
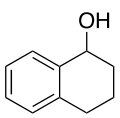
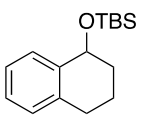
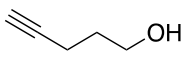
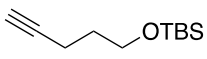
The new solvent-free microwave-assisted procedure for uridine (Scheme 2) was then applied to a panel of representative aliphatic and aromatic substrates (Table 2), including

alcohols of pharmaceutical interest such as eugenol (phenolic compounds), cholesterol (steroids), *L*-menthol and *trans*-sobrerol (terpenes), 4-pentyn-1-ol (alkyne).



Scheme 2. General procedure for solvent-free microwave-assisted *O*-silylation of uridine.

Table 2. Silylation of alcohols using the TBDMSCl/DBU/KNO_3 reagent system.

Entry	Starting Alcohol	Product	t (min)	Yield [a]
1			10	98%
2			5	82%
3			40	88%
4			30	86%
5			20	93%
6			5	84%
7			5	50%
8			10	81%
9			20	43%
10			5	62% [b]

Reaction conditions: Starting alcohol (0.3 mmol, 1.0 eq), TBDMSCl (0.4 mmol, 1.5 eq), KNO_3 (0.1 mmol, 0.3 eq), DBU (0.8 mmol, 2.7 eq), 75 °C, MW. [a] Isolated yield. [b] The reaction temperature was lowered to 60 °C due to the volatility of the starting material and the resulting silyl ether. Experimental details can be found in Supplementary Materials.

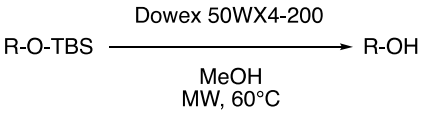
It is noteworthy that the reaction conditions allowed the silylation of sterically hindered *L*-menthol with a very good yield (entry **4**), which failed when performed in solution with the same reagent system and 2-methyltetrahydrofuran as solvent.

Trans-sobrerol was chosen to study the selectivity of the reaction when two differently hindered hydroxyl groups are simultaneously present. ^{1}H NMR experiments confirmed the formation of silyl ether **5** and no evidence of disilylated compound was observed, due to the steric hindrance of the tertiary hydroxyl group. Application on benzylic substrates was successful (entries **6** and **8**, 84% and 81% yield, respectively). The presence of an amino group in entry **8** was well tolerated, while the insertion of a 3-hydroxyl group in entry **7** gave a ratio of monosilylated and disilylated product of 3:1, indicating that both the phenolic group and the benzylic alcohol group compete for the silylation. Reaction of secondary alcohol in entry **9** required a longer time to react (20 min) and gave a moderate yield (43%), probably due to steric factors. The reaction conditions proved to be applicable also for the volatile alkyne **10** (62%). As for uridine protection, our sustainable solvent-free protocol proved to be effective for the panel of alcohols analyzed, eliminating hazardous reactants and solvents [8,27] and without the need of anhydrous procedures.

3.3. Microwave-Assisted Resin-Based Deprotection of a Panel of Silyl Ethers

As is well documented in literature, silyl ethers are typically cleaved with an excess of fluoride sources such as TBAF or KF, or under acidic conditions [3,28]. However, fluoride-mediated desilylation suffers from poor atom economy, due to the generation of waste fluorosilanes by-products [29]. In addition, the traditional THF/water/acid procedures usually suffer from lengthy reaction times, especially for bulkier silyl ethers such as TBS, TBDPS, or TIPS [30]. Some more environmentally friendly methods for silyl ether cleavage include examples with catalytic copper (II) salts [31,32], catalytic I_2 [14,33], SO_3H silica gel [34], alumina [35,36] kaolinite [37] and montmorillonite K-10 clay catalysis [38].

With the aim of developing also a green and mild silyl ether cleavage procedure which could benefit from either the use of reusable material or catalytic systems, various experiments with clay and resins were made on silyl ether **1**. Montmorillonite K-10 gave a 56% yield of deprotected uridine, and similar results were obtained when montmorillonite K-10 was used in combination with KF [39] (53% yield). Switching to resin-based cleavage, the same trend was observed with Amberlyst 15 (50% yield) while Dowex 50WX4-200 resin gave a good yield of 83% and was thus chosen as the standard deprotection method (Scheme 3).

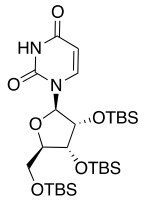
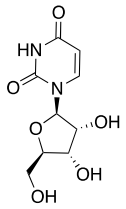
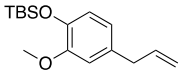
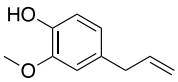
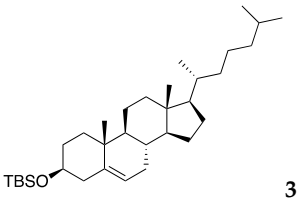
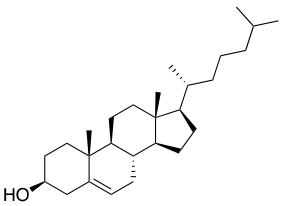
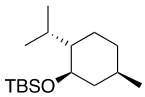
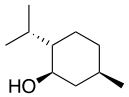
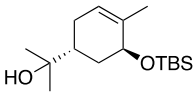
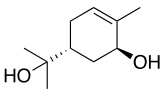


Scheme 3. General scheme for microwave-assisted resin-based silyl ether cleavage.

Cleavage of a representative panel of silyl ethers (compounds **1**–**5**) was thus accomplished with Dowex 50WX4-200 acidic resin in methanol under microwave irradiation [30] at 60 °C, as shown in Table 3, with fair to good yields. Only a minimum amount of methanol was required to allow proper swelling of the acidic resin. The products have been isolated by simple filtration, avoiding work-ups and in some cases purifications. Most importantly, the resin could be recycled and reused for a further cleavage step, reducing the associated costs.

Deprotection of persilylated uridine **D1** proceeded smoothly (83%), but a longer reaction time was required for a complete deprotection (100 min), while phenolic silyl ether **D2** and secondary cholesteryl silyl ether **D3** required shorter reaction times (20 min) for their cleavage, with fair to good yields (56% and 64%, respectively). As can be seen in entries **D4** and **D5**, deprotection of hindered or sensitive-to-acidic conditions silyl ethers was troublesome. In particular, in entry **D5**, the desired alcohol **5** was not isolated, due to the formation of a complex mixture of by-products in acidic conditions.

Table 3. Deprotection of the previously obtained silyl ethers **1**–**5** (Table 2) using the DowexWX4-200/MeOH reagent system.

Entry	Starting Alcohol	Product	t (min)	Yield [a]
D1	 **1**		100	83%
D2	 **2**		20	56%
D3	 **3**		20	64%
D4	 **4**		60	40%
D5	 **5**		40	/ [a]

Reaction conditions: silyl ether (1.0 mmol, 1.0 eq); Dowex 50WX4-200 (2:1 *w*/*w*), MeOH (0.5 mL), MW, 60 °C. [a] Silyl ether **5** reacts slower, leading to a complex mixture of by-products. The desired alcohol **D5** was not isolated. The reaction was carried out also at r.t. overnight to evaluate the influence of mild heating on the reaction outcome, but no changes were observed.

4. Conclusions

In conclusion, we optimized the classical *O*-silylation protocols for uridine, developing a novel, high-yielding, clean and simple solvent-free microwave-assisted procedure. The protocol proved to be scalable and applicable to a panel of alcohols with good-to-excellent yields. In contrast to the methods previously described [16], we were able to produce the target alcohols with shorter reaction times and without the use of hazardous solvents or toxic reagents. Most importantly, the setup is very simple, the reaction was carried out in the presence of air, and anhydrous conditions were not required differently from traditional protocols.

Subsequent silyl ether deprotection was accomplished via microwave-assisted resin-based cleavage, with fair-to-good yields, making the entire sequence of protection and deprotection steps facile and sustainable. Despite the fact that the deprotection step is applicable mainly to acidic stable compounds, the solvent-free silylation and resin-based deprotection are cleaner and simpler procedures for the introduction and removal of silyl ether protecting groups, useful for phenyl, benzyl and hindered alcohols.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/chemistry4040112/s1, synthetic procedures and NMR.

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