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SHORT COMMUNICATION

A SOLVENT FREE AND SELECTIVE METHOD FOR PREPARATION OF TRIPHENYLMETHYL ETHERS OF ALCOHOLS AND NUCLEOSIDES

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ABSTRACT. A very simple and efficient method is described for protection of alcohols and nucleosides with trityl(triphenylmethyl), mono and dimethoxytrityl chlorides in the presence of triethylamine under microwave irradiation. High selectivity was observed for tritylation of 5'-OH function of nucleosides.

KEY WORDS: Protection, Trityl chlorides, Microwave irradiation, Nucleosides, Selectivity

INTRODUCTION

Hydroxyl group protection is important in the synthesis of some organic molecules. One way to protect hydroxyl groups is to transform the molecules to their corresponding trityl (Tr) ethers. In general, the sterically least hindered alcohols are the most readily tritylated. A large number of tritylation methods exist for the introduction of the trityl group into a variety of alcohols [1-10]. Due to its steric hindrance, trityl group finds a specific application and can be used for selective protection in different substrates such as selective protection of hydroxyl groups in nucleosides. On the other hand, trityl ethers show good stability in mild acidic or basic media which make them good candidates to be used in total syntheses of related targets. The generally used procedure for the preparation of trityl ethers involves treatment of alcohols with trityl chlorides in the presence of pyridine as a base and solvent [11, 12]. This method requires pyridine as a solvent that is a toxic compound with high boiling point, and needs an aqueous work-up. In addition this method suffers from prolonged reaction time. The 4,4´-dimethoxytrityl (DMT) group is an exceedingly useful control element in organic synthesis [1, 13]. In a study on the selective protection of hydroxyl groups in ribonucleosides, 4,4´-dimethoxytrityl chloride reacts almost exclusively with the primary 5´-hydroxyl function [14, 15]. Several advantages can be envisioned for the use of the 4,4´-dimethoxytrityl group as a hydroxyl protecting moiety: (1) low cost and ready availability of pure 4,4´-dimethoxytrityl chloride (DMTCl), (2) greater stability of 4,4´-dimethoxytrityl ethers than 4,4´,4´´-trimethoxytrityl (TMT) ethers, (3) more facile acidic deprotection of dimethoxytrityl ethers than trityl ethers, and (4) selective protection of 5´-hydroxyl of ribonucleosides with 4,4´-dimethoxytrityl chloride. In recent years, the use of microwave irradiation in organic reactions is rapidly increasing, because of its short reaction times and operational simplicity. It has been reported that a variety of reactions such as formation of acetals [16], N-alkylation reactions [17], oxidation reactions [18], condensation reactions [19], could be facilitated by microwave irradiation as a good energy transferring medium.

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Due to the importance of selective protection of hydroxyl groups in the synthesis of nucleosides under mild conditions, and to overcome the above-mentioned problems, more work is needed in this field.

EXPERIMENTAL

The chemicals were either prepared in our laboratories or purchased from Fluka (Switzerland) or Merck (Germany) chemical companies. All yields refer to isolated products after column chromatography. The products were characterized by their spectral data. IR spectra were recorded on a Perkin Elmer 781 spectrometer (USA). NMR spectra were recorded on a Bruker advanced DPX-250 MHz, FT-NMR spectrometer (USA). Mass spectra were recorded on a Shimadzu GC MS-QP 1000 EX (Japan). All reactions were carried out using domestic microwave oven (National, 2450 MHz, Japan). Melting points were determined on a Buchi 510 (Switzerland) in open capillary tubes circulating oil melting point in open apparatus and are uncorrected. The purity of the substance and the progress of the reactions were accomplished by TLC on silica gel polygram SILG/UV254 plates. Column chromatography was carried out on the medium column of silica gel 60 Merck (30-270 mesh) in glass column (1 or 2 cm diameter) using 10-20 grams of silica gel per one gram of mixture.

Protection of alcohols with trityl chloride/triethylamine under microwave irradiation; general procedure. A beaker was charged with, in succession, trityl chloride (3.34 g, 12 mmol), triethylamine (3.5 mL, 25 mmol) and the alcohol substrate (10 mmol) and then it was irradiated with 300-700 W power of domestic microwave. The completion of the reaction was monitored by TLC. The reaction mixture solidified on cooling to room temperature. Then the reaction mixture was dissolved in $CHCl_3$ (100 mL) and washed with 5% $NaHCO_3$ (60 mL). The organic layer was separated and washed with water (2 × 50 mL). The organic solvent was dried with anhydrous Na_2SO_4. The solvent was evaporated and the residue was chromatographed on a short column of silica gel using petroleum ether as eluent. The pure trityl ether was obtained in 65-96% yield (Table 2). The products were isolated and identified by spectral data (^{1}H NMR, IR, and MS) or comparison with authentic samples.

*Protection of diphenylmethanol(**1f**) with dimethoxytrityl chloride/triethylamine under microwave irradiation as a typical procedure.* In a beaker, a mixture of dimethoxytrityl chloride (4.06 g, 12 mmol) and triethylamine (3.5 mL, 25 mmol) was taken and diphenylmethanol **1f** (1.84 g, 10 mmol) was added to this mixture and was irradiated with 500 W power of domestic microwave. The completion of the reaction was monitored by TLC. The reaction mixture was solidified on cooling to room temperature. Then the reaction mixture was dissolved in $CHCl_3$ (100 mL) and washed with 5 % $NaHCO_3$ (60 mL). The organic layer was separated and extracted with water (2 × 50 mL). The organic solvent was dried with anhydrous Na_2SO_4. The solvent was evaporated and the residue was chromatographed on a short column of silica gel using petroleum ether as eluent. The pure diphenylmethyl dimethoxytrityl ether **2f** was obtained as a white solid in 80% yield; m.p. 79-81 °C; $R_{f[(EtOAc:n\text{-}Hexane)\ 2:8]} = 0.6$. ^{1}H NMR δ 7.49-6.91 (23 H, m, Ph-), 5.36 (1H, s, CH-), 3.77 (6H, s, CH_3-).

*Selective protection of 1,2-propanediol (**1n**) with dimethoxytrityl chloride and triethylamine under microwave irradiation.* In a beaker, a mixture of dimethoxytrityl chloride (4.06 g, 12 mmol) and triethylamine (3.5 mL, 25 mmol) was taken and 1,2-propanediol **1n** (0.76 g, 10 mmol) was added to this mixture and was irradiated with 500 W power of domestic microwave. The completion of the reaction was monitored by TLC. The reaction mixture was solidified on cooling to room temperature. Then the reaction mixture was dissolved in $CHCl_3$ (100 mL) and

washed with 5% $NaHCO_3$ (60 mL). The organic layer was separated and extracted with water (2 × 50 mL). The organic solvent was dried with anhydrous Na_2SO_4. The solvent was evaporated and the residue was chromatographed on a short column of silica gel using petroleum ether as eluent. The pure 2-hydroxy-1-dimethoxytrityloxypropane **2n** was obtained as a white solid in 85% yield; m.p. 98-100 °C; $R_{f[(EtOAc:n\text{-}Hexane)\ 2:8]} = 0.34$. ^{1}H NMR δ 7.36-6.86 (13 H, m, Ph-), 4.82 (1H, s, OH) 3.91 (6H, s, CH_3O) 3.75 (1H, m, CH) 3.60 (2H, d, CH_2-), 1.35 (3H, d, CH_3-).

Selective protection of 5′-OH of nucleosides with dimethoxytrityl chloride and triethylamine under microwave irradiation; general procedure. In a beaker, a mixture of nucleoside (1 mmol) and triethylamine (0.35 mL, 2.5 mmol) was taken and dimethoxytrityl chloride (0.4 g, 1.2 mmol) was added to this mixture and was irradiated with 700 W power of domestic microwave. The completion of the reaction was monitored by TLC. The reaction mixture was solidified on cooling to room temperature. Then the reaction mixture was dissolved in ethylacetate (50 mL) and washed with 5% $NaHCO_3$ (40 mL). The organic layer was separated and extracted with water (2 × 30 mL). The organic solvent was dried with anhydrous Na_2SO_4. The solvent was evaporated and the crude product was chromatographed on a short column of silica gel using petroleum ether for removal of dimethoxytrityl alcohol, then with $CHCl_3$-CH_3OH (9:1) to give the corresponding protected 5′-O-dimethoxytrityl nucleoside in 45-83% yield (Table 3). The products were isolated and identified by spectral data (^{1}H NMR, IR, MS) or comparison with authentic samples.

*Selective protection of 5′-OH of adenosine (**3b**) with dimethoxytrityl chloride/triethylamine under microwave irradiation*. In a beaker, a mixture of adenosine **3b** (0.267 g, 1 mmol) and triethylamine (0.35 mL, 2.5 mmol) was taken and dimethoxytrityl chloride (0.4 g, 1.2 mmol) was added to this mixture and was irradiated with 700 W power of domestic microwave. The completion of the reaction was monitored by TLC. After the reaction was completed, the reaction mixture was solidified on cooling to room temperature. Then the reaction mixture was dissolved in ethylacetate (50 mL) and washed with 5% $NaHCO_3$ (40 mL). The organic layer was separated and extracted with water (2 × 30 mL). The organic solvent was dried with anhydrous Na_2SO_4. The solvent was evaporated and the crude product was chromatographed on a short column of silica gel using petroleum ether for removal of dimethoxytrityl alcohol, then with $CHCl_3$-CH_3OH (9:1), so the corresponding protected 5′-O-dimethoxytrityl adenosine **4b** was obtained as a white solid in 60% yield; m.p. 145-147 °C (lit [14] 145-146 °C); $R_{f[(CHCl3\text{-}CH3OH)\ 9:1]} = 0.17$; mass spec. m/z 570 $(M+H)^+$; ^{1}H NMR. δ 8.2 (1H, s, H-8), 8.07 (1H, s, H-2), 6.7-7.35 (15 H, m, 2H, NH_2, ph-DMT-), 5.9 (1 H, d, H-1'), 5.5 (1 H, d, OH- 2'), 5.15 (1 H, d, OH-3'), 4.63 (1 H, m, H-2'), 4.28 (1 H, m, H-3'), 4.1 (1 H, m, 4-'), 3.68 (6 H, s, OCH_3), 3.2 (2 H, m, H-5').

RESULTS AND DISCUSSION

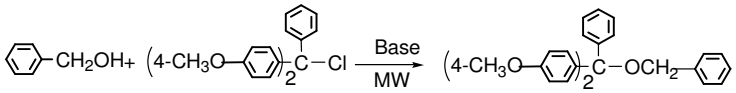
We have already reported selective protection of alcohols and phenols with triisopropylsilyl chloride under microwave irradiation in the presence of imidazole [20]. In this paper, we report a mild and efficient method for hydroxyl group protection by reaction of 1°, 2° and 3° alcohols with trityl chloride and its derivatives in the presence of triethylamine under microwave irradiation in the absence of solvent.

Various alcohols were subjected to the tritylation reaction in the presence of triethylamine under microwave irradiation. To see the effect of different bases on the progress of this reaction, we examined several bases other than triethyamine for the tritylation of benzyl alcohol (BnOH) (Table 1). The reaction is outlined in (Scheme 1).

Table 1. Effect of different bases for the protection of benzyl alcohol with dimethoxytrityl chloride using microwave irradiation.

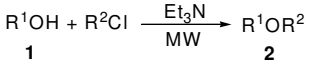
Base	Time (min)	Power (watt)	Yield (%)[a]
Al_2O_3 (basic)	5 min	700	10
DBU	5 min	700	25
Imidazole	5 min	700	40
Et_3N	1 min	300	92

[a] Yields were on the basis of products isolated from column chromatography.



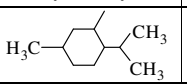
Scheme 1. Bases: Al_2O_3, 1,8-diazabicyclo[5.4.0.] undec-7-ene(DBU), imidazole, Et_3N; molar ratios of the reactants: BnOH:DMTCl:Base (1:1.2:2.5).

The mixture of alcohol and triethylamine was reacted with trityl chloride (or its derivatives) in molar ratio of (1:2.5:1.2), respectively (Scheme 2). TLC monitoring indicated that all of the alcohol consumed and one product was produced. The results of protection of different alcohols are shown in Table 2. As it is shown, aliphatic and benzylic alcohols are protected very easily by this method with excellent yields.



Scheme 2. Molar ratios of the reactants: $R^1OH:R^2Cl:Et_3N$ (1:1.2:2.5).

Table 2. Protection of different alcohols with trityl chloride (or its derivatives).

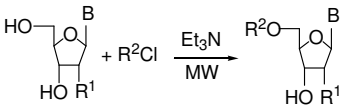
Substrate	R^1	R^2	Product[a]	Power (watt)	Time (s)	Yield (%)[b]
1a	$PhCH_2$-	DMT	2a	300	45	92
1b	4-$CH_3OC_6H_4CH_2$-	DMT	2b	300	20	96
1c	4-$NO_2C_6H_4CH_2$-	DMT	2c	300	20	90
1d	$PhCH_2CH_2CH_2$-	DMT	2d	300	60	90
1e	$PhCH(CH_3)$-	DMT	2e	500	30	85
1f	$(Ph)_2CH$-	DMT	2f	500	60	80
1g	Cyclohexyl	DMT	2g	300	50	90
1h		DMT	2h	300	50	90
1i	$PhCH_2$-	MMT	2i	300	50	92
1j	$PhCH_2CH_2CH_2$-	MMT	2j	500	120	75
1k	$(Ph)_2CH$-	MMT	2k	700	60	82
1l	Cyclohexyl	MMT	2l	500	60	85
1m	$PhCH_2$-	Tr	2m	700	120	65
1n	$CH_3CH(OH)CH_2$-	DMT	2n	700	60	85
1o	$(Ph)_2C(CH_3)$-	DMT	2o	700	120	75

[a] The products were characterized by ^1H NMR, IR, UV or comparison with the authentic samples. [b] Yields were on the basis of products isolated from column chromatography.

An interesting feature of the present method is the conversion of tertiary alcohols such as 1,1-diphenyl ethanol **1o** to its corresponding dimethoxytrityl ether **2o** in 75% yield in 120 s and 700 watt.

In order to show more usefulness of this method, selective dimethoxytritylation of 1,2-propanediol was also investigated. By using this method, we were able to obtain 2-hydroxy-1-dimethoxytrityloxypropane **2n** in 85% yield.

Due to the importance of selective protection of nucleosides hydroxyl groups, we further applied this method for the protection of hydroxyl groups in these compounds. Reaction of nucleosides **(3a-f)** with trityl, 4-monomethoxy and 4,4'-dimethoxytrityl chloride (R^2Cl) with molar ratio of 1:1.2 in the presence of Et_3N (2.5 eq) under microwave irradiation in 700 watt afforded the corresponding trityl ethers **(4a-f)**. It should be noted that, purine's bonds are only sensitive in acidic media and in our reported protocol, no bond cleavage were detected in the presence of Et_3N and microwave irradiation. The reactions are outlined in (Scheme 3).



3 **4**

Scheme 3. Substrates and reagents: (a) R^1 = OH, B = uracil, R^2 = DMT (b) R^1 = OH, B = adenine, R^2 = DMT (c) R^1 = OH, B = uracil, R^2 = MMT (d) R^1 = H, B = thymine, R^2 = MMT (e) R^1 = OH, B = adenine, R^2 = Tr (f) R^1 = OH, B = uracil, R^2 = Tr. Molar ratios of substrate/R^2Cl/Et_3N are (1:1.2:2.5), respectively.

The results for the protection of nucleosides are shown in Table 3. By this method, 5´-hydroxyl function of uridine was easily protected with dimethoxytrityl chloride in 78% yield **(4a)**. In comparison, when we repeated the literature method for this protection in pyridine, 5´-hydroxyl function of uridine was protected in 54% yield after 72 h [13].

Table 3. Protection of nucleosides with trityl chlorides under microwave irradiation in the presence of triethylamine with molar ratio of (1:1.2:2.5), respectively.

Substrate	Product[a]	Time (s)	Yield (%)[b]	M.p. (°C)	M.p. (°C) [Ref.]
3a	**4a**	60	78	122-123	123-124 [13]
3b	**4b**	90	60	145-147	145-146 [21]
3c	**4c**	90	75	103	103-105 [13]
3d	**4d**	90	83	102-104	103-105 [12]
3e	**4e**	180	45	129-131	130-131 [22]
3f	**4f**	120	65	95	95-97 [22]

[a] The products were characterized by ^{1}H NMR, IR, UV or comparison with the authentic samples. [b]Yields were on the basis of products isolated from columnchromatography.

In conclusion, by use of microwave irradiation, we modified general procedure for selective tritylation of nucleosides and alcohols and took a short cut with respect to the previous protocols [13]. Elimination of pyridine as a toxic solvent, high yields of the products accompanied with high selectivity and easy work-up procedure are worthy of mention as advantages for laboratory and large-scale operation of this method. In addition, no N-tritylated side product occurred in the protection reactions of nucleosides. We believe that the presented method, which is very simple and offers high yields of the tritylated products, is more useful than the available procedures for protection of alcohols and nucleosides with mono and dimethoxytrityl chloride.

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