Microwave Assisted Synthesis of *S*-Trityl and *S*-Acylmercaptoalkanols, Nucleosides and Their Deprotection

P. Kumar and K.C. Gupta*
Nucleic Acids Research Laboratory, Centre for Biochemical Technology, Mall Road, Delhi University Campus, Delhi- 110 007, India

(Received March 14, 1996)

Simple and high yielding methods for the synthesis and deprotection of S-trityl and S-acylhexanols and appropriately protected 2'-deoxynucleosides in solvent and dry media conditions are described which occur under mild conditions using microwave irradiation.

Simple chemical strategies required for the synthesis and deprotection of S-acyl and S-tritylmercaptoalkanols and appropriately protected 2'5'-dideoxy-5'-mercaptonucleosides make them interesting candidates for the synthesis of 5'-modified-oligonucleotides, required for molecular biological studies. Organic reactions under microwave irradiation are at present under extensive examination.[1-10] As a part of our programme related to the development of reagents for oligonucleotide synthesis and modifications, we report here a novel strategy for the synthesis and deprotection of S-trityl and S-acylhexanols and appropriately protected 2',5'-dideoxy-5'-mercaptonucleosides under microwave irradiation. The synthesis and deprotection of S-trityl and S-acyl derivatives of 6-mercaptohexanol and appropriately protected 5'-mercapto-2'-deoxynucleosides have been studied in solution and dry media conditions under microwave irradiation and compared them with the corresponding reactions carried out under conventional thermal treatment.[11-13]

$$\mathbf{RCOSK + R'\text{-}X \xrightarrow{\mu\sim} RCOS\text{-}R' + KX}$$

R = Ph, Me; R' = Alkanol or 2'-deoxynucleoside; X = Br or I

In solution phase, S-acylation proceeded in quantitative yields in just 30s (Table-1) under microwave irradiation. S-Tritylation also proceeded fast with 85 to 90% yields depending upon the use of mercaptotritan or its sodium salt (Table-1). These reactions were then studied in dry media conditions employing a number of solid supports. S-Acylation reaction (Table-2) on neutral and basic alumina completed in 2-3 min with quantitative yields. However, the yields of S-acylhexanol were only 75-80% on silica support and did not improve even on prolonged reaction time. S-Tritylation also proceeded well on neutral and basic alumina when sodium salt of mercaptotritan was employed. Unlike solution phase, the yields of S-tritylation in dry media did not exceed to 40% when used in conjunction with sodium hydroxide or DBU.

Deprotection studies were carried out only with S-acyl derivatives as S-trityl derivatives need reductive conditions and involve two step process. Two types of deprotecting reagents as shown in Table-3 were employed for this purpose. Both of the reagents have been found to be equally effective to bring about deprotection in 28-50s.

Table1.Synthesis of S-acyl and S-tritylalkanols in solution phase

	I	II	Yield %	Time	T_{conv} / T_{MW}
1)	CH_3COSK (DMF)	$Br(CH_2)_6OH$	conv. - 100 MW - 100	180 min 30 sec	360
2)	C_6H_5COSK (DMF)	$Br(CH_2)_6OH$	conv. - 100 MW - 100	180 min 30 sec	360
3)	TrSNa (DMF)	$Br(CH_2)_6OH$	conv. - 79 MW - 90	60 min 40 sec	90
4)	TrSH+NaOH (Ethoxyethanol)	$Br(CH_2)_6OH$	conv. - 55 MW - 85	30 min 30 sec	60
5)	C_6H_5COSK (DMF)	5'-IdT	MW - 100	30 sec	-
6)	CH_3COSK (DMF)	5'-IdT	MW - 100	30 sec	-
7)	C_6H_5COSK (DMF)	5'-IdG^{ibu}	MW - 100	50 sec	-
8)	CH_3COSK (DMF)	5'-IdG^{ibu}	MW - 100	50 sec	-
9)	TrSNa (DMF)	5'-IdG^{ibu}	MW - 65	70 sec	-
10)	TrSNa (DMF)	5'-IdT	MW - 70	60 sec	-

5'-IdT : 2',5'-dideoxy-5'-iodothymidine; 5'-IdGibu : N^2-Isobutyryl-2',5'-dideoxy-5'-iodoguanosine.

Table 2. Synthesis of S-acyl and S-tritylalkanols in 'dry media'

I	II	Support	Yield %	Time
1) CH_3COSK	$Br(CH_2)_6OH$	Alumina (N)	100	3 min
		Alumina (B)	100	3 min
		Silica	75	2 min
2) C_6H_5COSK	$Br(CH_2)_6OH$	Alumina (N)	100	2 min
		Alumina (B)	100	3 min
		Silica	80	2 min
3) TrSNa	$Br(CH_2)_6OH$	Alumina (N)	90	5 min
		Alumina (B)	90	5 min
4) TrSH+NaOH	$Br(CH_2)_6OH$	Alumina (N)	40	2 min
		Florisil	44	2 min
5) TrSH+DBU	$Br(CH_2)_6OH$	Alumina (N)	40	2 min
		Alumina (B)	40	3 min
6) CH_3COSK	5'-IdT	Alumina (N)	100	3 min
		Alumina (B)	100	3 min
7) C_6H_5COSK	5'-IdGibu	Alumina (N)	100	3 min

Alumina (N) : Alumina (Neutral); Alumina (B) : Alumina (Basic).

A. General procedure for synthesis in solution. In a loosely capped vial, potassium thioacetate (1.2 mmol) and 6-bromohexanol or appropriately protected 2',5'-dideoxy-5'-iodo- (N-protected) - nucleoside (1 mmol) were mixed together in N,N-dimethylformamide (2 ml). The reaction vial was then kept inside a domestic microwave oven (Kelvinator, India) and irradiated for 10s at high power (2450 Hz, 700W), cooled to room temperature and reirradiated for

Table 3.

	Deprotection (%)	Time
0.2M NaOH in Dioxane : Water (1:1, v/v, 2 ml)		
1) $CH_3COS(CH_2)_6OH$	100	28 sec
2) $C6H_5COS(CH_2)_6OH$	100	35 sec
0.5M K2CO3 in Water : Dioxane : MeOH (1: 0.5 : 0.5, v/v/v, 2 ml)		
1) $CH_3COS(CH_2)_6OH$	100	35 sec
2) $C_6H_5COS(CH2)_6OH$	100	49 sec

10s. None of the reactions were irradiated longer than 10s at a time to avoid boiling off the solvent. Progress of the reaction was monitored after each exposure. After completion of the reaction, solvent was removed under reduced pressure and the material was isolated and purified following reported procedure desribed for conventional thermal method.[11] The compounds were fully characterized and compared with the authentic samples prepared by conventional method. Other reactions were also carried out in similar way.

B. General procedure for synthesis in 'dry medium'. Potassium thioacetate (1.2 mmol) and 6-bromohexanol (1 mmol) were dissolved in dichloromethane (1 ml). appropriate alumina (1g) was added and swirled for a while followed by removal of solvent under gentle vacuum. The solid matrix so obtained was kept in a loosely capped vial, irradiated in microwave oven (Table-2) for 1 min, cooled to room temperature and reirradiated till reaction cmpleted. None of the reactions were irradiated for longer than 1 min. After complete reaction, the desired material was isolated and purified as reported in conventional methods.[11]

General procedure for deprotection of S-acyl group. Deprotection of S-acyl (acetyl and benzoyl) was carried only with S-acylmercaptohexanol derivatives in two solvent systems as mentioned in Table-3. The deprotection was performed in similar way as described under synthesis procedure **A** except that irradiation time was kept at 7sec at a time. The deprotected desired material was isolated, purified and characterized in analogous way to conventional method.

In conclusion we have established simple conditions for the synthesis and deprotection of S-acyl and S-tritylmercaptoalkanols and appropriately protected 2',5'-dideoxy-5'-mercapto-2'5'-dideoxynucleosides under microwave irradiation.

The financial support from the Department of Biotechnology, N. Delhi is gratefully acknowledged.

References

1 R.J. Giguere, T.L. Bray, and S.M. Duncan, *Tet. Lett.*, 4945 (1986).

2 R.N. Gedye, W. Rank,and K.C. Westaway, *Can. J. Chem.*, 69, 706 (1991).

3 A.K. Bose, M.S. Manhas, B.K. Banik,and E.W. Robb, *Res. Chem. Intermed.* 20, 1 (1994).

4 R.S. Varma, A.K. Chaterjee,and M. Varma, *Tet. Lett.*, 3207 (1993).

5 R.S. Varma and M. Varma, *Tet. Lett.*, 33, 5937 (1992).

6 D. Villemin and A.B. Alloum, *Synth. Commun.*, 21, 63 (1991).

7 R.S. Varma, J.B. Lamture,and M. Varma, *Tet. Lett.*, 3029 (1993).

8 J.A. Hesek and R.C. Wilson, *Anal. Chem.*, 46, 1160 (1974).

9 D.-R. Hwang, S.M. Moerlein, L. Lang,and M.J. Welch, *J. Chem. Soc., Chem. Commun.*, 1799 (1987).

10 D. Michael, P. Mingos,and D.R. Baghurst, *Chem. Soc. Rev.*, 20, 1 (1991).

11 Connolly, *Nucl. Acids Res.*, 13, 4485 (1985).

12 W.H.A. Kuijpers and C.A.A. van Boeckel, *Tetrahedron*, 49, 10931 (1993).

13 P. Kumar, D. Bhatia, R.C. Rastogi,and K.C. Gupta, *BioMed. Chem. Lett.*, 6, 683 (1996).

14 L. Zervas, I. Photaki,and N. Ghelis, *J. Am. Chem. Soc.*, 85, 1337 (1963).