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Efficient Method for Tetrahydropyranylation of Phenols and Alcohols Using 2,4,6-Trichloro[1,3,5]triazine

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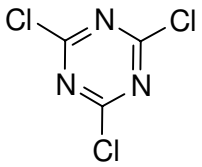
Alcohols and phenols were tetrahydropyranylated in the presence of 2,4,6-trichloro[1,3,5]triazine in good to excellent yields in acetonitrile.

Key Words: 2,4,6- Trichloro[1,3,5]triazine (TT), cyanuric chloride (CC), alcohol, phenol, tetrahydropyranylation, 3,4-dihydro- 2H-pyran (DHP), protection.

Introduction

Because of the easy preparation and good stability of tetrahydropyranyl groups in the presence of hydrides, alkylating agents, Grignard reagents, organometallic reagents, etc.,[1] they are frequently used for the protection of alcohols and phenols. In addition, they serve as stable protecting groups in peptide, nucleoside, nucleotide, carbohydrate and steroid chemistry. Tetrahydropyranylation of alcohols can be accomplished by using *p*-TSA,[2] $BF_3.OEt_2$,[3] and PPTS.[4] Recently, some developed reagents have been used for this purpose such as $ZrCl_4$,[5] I_2,[6] LiBr,[7] acetonyltriphenylphosphonium bromide (ATPB),[8] TBATB,[9] aluminum chloride hexahydrate,[10] $In(Oft)_3$,[11] alkylimidazolium tetrachloroaluminates,[12] $InCl_3$ immobilized in ionic liquids,[13] and bromodimethylsulfonium bromide.[14]

The problems associated with some of these procedures, such as handling of reagents due to their environmental hazards, incompatibility with acid sensitive functional groups,[3,9,10,13] using expensive and water sensitive catalysts or reagents, and catalyst preparation prior to use[4,8,9,14] prompted our interest in the development of an alternative procedure using 2,4,6-trichloro[1,3,5]triazine **I.** The use of this reagent has been reported for the conversion of carboxylic acids into chlorides, esters, amides, peptides and macrolactones,[15,16] mild and selective reduction of carboxylic acids,[17] synthesis of α-diazoketones,[18] deoxygenation of sulfoxides,[19] synthesis of β-lactams,[20] formylation of alcohols,[21] modified Swern oxidation of alcohols,[22] conversion of alcohols to halides,[23] and oxidative coupling of thiols to disulfides.[24] These observations encouraged us to test the ability of 2,4,6- trichloro[1,3,5] triazine for the protection of hydroxyl groups with 3,4-dihydro-2H-pyran. We report the successful tetrahydropyranylation of primary secondary and tertiary alcohols and phenols under mild reaction conditions using 2,4,6-trichloro[1,3,5] triazine.



I

Experimental

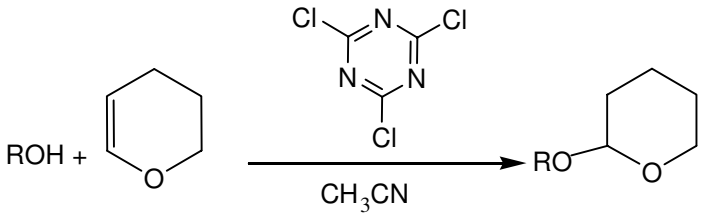
The chemicals were obtained from Merck and Fluka. FT-IR spectra were recorded on a Perkin Elmer RXI spectrometer. NMR spectra were recorded on a Bruker Avance DPX 250 MHz spectrometer. The products were purified by column chromatography and the purity determination of the products was accomplished by GLC on a Shimadzu model GC 10-A using n-octane as internal standard or by thin layer chromatography on silica gel polygram on SIL G/UV 254 plates.

Typical procedure for the protection of benzyl alcohol

To a mixture of benzyl alcohol (1 mmol, 0.108 g) and DHP (1 mmol, 0.084 g) in dry CH_3CN (3-5 mL) was added TT (1 mmol, 0.184 g), and the resulting mixture stirred at room temperature for 20 min. The reaction mixture was filtered. Column chromatography of the filtrate on silica-gel using n-hexane as eluent gave benzyl tetrahydropyranyl ether in 98% yield.

Results and Discussion

In continuation of our studies on the protection of hydroxyl groups[25−27] and some applications of 2,4,6-trichloro[1,3,5] triazine in organic synthesis,[28,29] we investigated the tetrahydropyranylation of alcohols and phenols in the presence of 2,4,6- trichloro[1,3,5] triazine. First, the protection of benzyl alcohol in the presence of 2,4,6-trichloro[1,3,5]triazine was studied. Benzyl tetrahydropyranyl ether was produced after 20 min in quantitative yield. Then we applied these conditions for the protection of structurally different alcohols and phenols (Scheme).



R : primary, secondary, tertiary alkyl and phenyl

Scheme

In order to optimize the reaction conditions, we first examined the effect of different molar ratios of ROH/DHP/TT. Employing the ratios shown in Table 1 the best results were obtained and tetrahydropyranyl ethers were produced in good to excellent yields. The ^{13}C-NMR signal between 57.6 and 67.9 ppm due to the C-O-THP group and the strong absorption band between 1300 and 1000 cm^{-1} is attributed to the C-O stretching of C-O-THP ethers in the IR spectrum.

As shown in Table 1, this method is very suitable for the protection of various types of alcohols and phenols, providing a novel application of 2,4,6- trichloro[1,3,5]triazine in organic synthesis.

Table 1. Preparation of THP ethers in the presence of 2,4,6- trichloro [1,3,5]triazine.

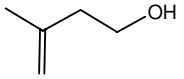
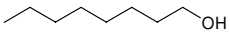
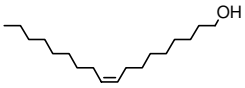
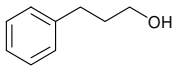
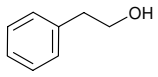
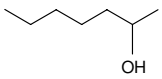
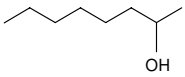
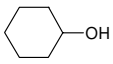
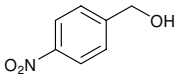
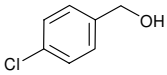
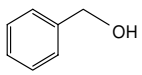
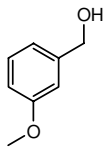
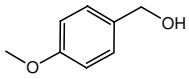
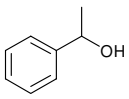
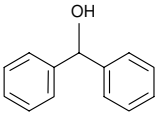
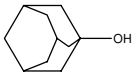
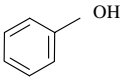
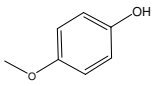
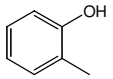
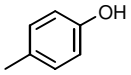
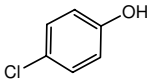
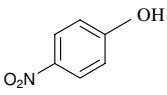
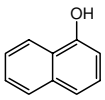
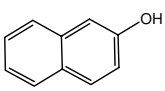
Entry	ROH	Molar Ratio ROH/DHP/TT	Time(h)	Conversion % [a]	Isolated Yield %
1		1/1/1	8.5	100	92
2		1/1/1	8	100	90
3		1/1/1	7.5	100	93
4		1/1/1	7	100	96
5		1/1/1	8	100	98
6[b]		1/1/2	45	100	96
7[b]		1/1/2	43	100	98
8[b]		1/1/2	44	100	97
9		1/1/1.2	24	90	85
10		1/1/1.2	24	100	92
11		1/1/1	20(min)	100	98
12		1/1/1	6	100	95
13		1/1/1	35(min)	100	95

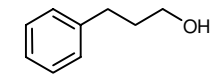
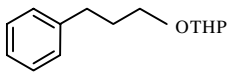
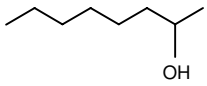
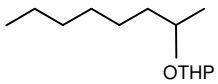
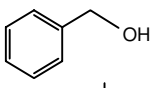
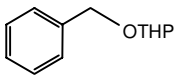
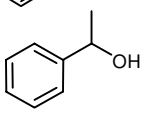
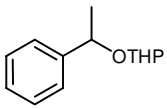
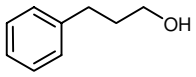
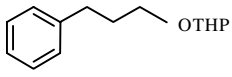
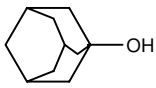
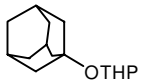
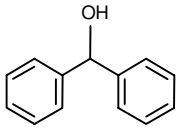
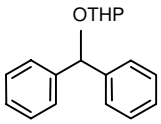
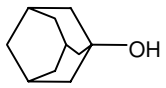
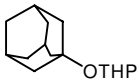
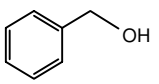
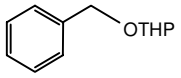
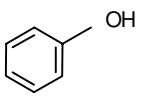
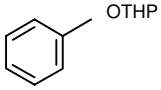
Table 1. Continued.

Entry	ROH	Molar Ratio ROH/DHP/TT	Time(h)	Conversion % [a]	Isolated Yield %
14		1/1/1	3.5(h)	100	99
15[b]		1/1/2	28	100	90
16[b]		1/1/2	34	90	68
17[b]		1/1/2	30	85	70
18[b]		1/1/2	10.5	100	95
19[b]		1/1/2	8	100	97
20[b]		1/1/2	9	100	90
21[b]		1/1/2	9	100	94
22[b]		1/1/2	22	100	95
23[b]		1/1/2	54	100	98
24[b]		1/1/2	24	80	73
25[b]		1/1/2	24	60	52

[a] GC yield using internal standard., [b]The reaction was performed under reflux

This method was found to be highly selective for primary alcohols. In a binary mixture of 3-phenyl-1-propanol and 2-octanol, the primary alcohol was completely converted to corresponding tetrahydropyranyl ether, while less than 5% conversion was observed for the secondary alcohol (entry 1, Table 2). Similarly, excellent selectivity was observed for tetrahydropyranylation of benzyl alcohol in the presence of 1-phenyl ethanol (entry 2, Table 2); 1° and 2° alcohols were selectively converted to tetrahydropyranyl ethers in the presence of a 3° alcohol (entries 3 and 4, Table 2). Furthermore, this method showed excellent selectivity in the tetrahydropyranylation of alcohols in the presence of phenols (entry 5, Table 2).

Table 2. Selective reaction of different binary mixtures with DHP/TT.

Entry	Binary Mixture	Products	Time (h)	Yield %[a]
1[b]			31	94
				5
2[b]			2	95
				2
3[b]			20	97
				3
4[c]			28	98
				2
5[b]			3.5	96
				3

[a]GC yield using internal standard . [b]ROH/DHP/TT=1/1/1 . [c]ROH/DHP/TT=1/1/2.

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References

1. T.W. Greene and P.G.M. Wuts, "**Protective Groups in Organic Synthesis"**, 3rd Ed. John Wiley: New York, 1999.
2. (a) E.J. Corey, H. Niwa and J. Knolle, **J. Am. Chem. Soc. 100,** 1942-43 (1978).
   (b) K.F. Bernady, M.B. Floyd, J.F. Poletto and M.J. Weiss, **J. Org. Chem. 44,** 1438-47 (1979).
3. H. Alper and L. Dinkes, **Synthesis** 81-82 (1972).
4. M. Miyashita, A. Yoshikoshi and P.A. Grieco, **J. Org. Chem, 42**, 3772-74 (1977).
5. N. Rezai, F.A. Meybodi and P. Salehi, **Synth. Commun. 30**, 1799-05 (2000).
6. N. Deka and J.C. Sarma, **Synth. Commun. 30**, 4435-41 (2000).
7. M.A. Reddy, L.R. Reddy, N. Bhanumathi and K.R. Rao, **Synth. Commun. 30**, 4323- 28 (2000).
8. Y.S. Hon and C.F. Lee, **Tetrahedron Lett. 40**, 2389 (1999).
9. S. Naik, R. Gopinath and B.K. Patel, **Tetrahedron Let. 42**, 7679-81 (2001).
10. V.V. Namboodiri and R.S. Varma, **Tetrahedron Lett. 43**, 1143-46 (2002).
11. T. Mineno, **Tetrahedron Lett. 43**, 7975-7978 (2002).
12. V.V. Namboodiri and R.S. Varma, **Chem. Commun**. 342-3 (2002).
13. J.S. Yadav, B.V. Subba Reddy and D. Gnaneshwar, **New J. Chem. 27**, 202-4 (2003).
14. A.T. Khan, E. Mondal, B.M. Borah and S. Ghosh, **Eur. J. Org. Chem**. **21**, 4113-17 (2003).
15. K. Venkataraman and D.R. Wagle, **Tetrahedron Lett**. **20**, 3037-3040 **(**1979).
16. K. Venkataraman and D.R. Wagle, **Tetrahedron Lett. 21**, 1893-96 (1980).
17. M. Falorini, A. Porcheddu and M. Tadder, **Tetrahedron Lett. 40**, 4395-96 (1999).
18. D.C. Forbes, E.J. Barrett, D.L. Lewis and M.C. Smith, **Tetrahedron Lett. 41**, 9943-47 (2000).
19. M.S. Manhas, A.K. Bose and M.S. Khajavi, **Synthesis** 209-10 (1981).
20. G.A. Olah, A.P. Fung, B.G.B. Gupta and S.C. Narang, **Synthesis** 221 (1980).
21. L. De Luca, G. Giacomelli and A. Porcheddu, **J. Org. Chem. 67,** 5152-55 (2002).
22. L. De Luca, G. Giacomelli and A. Porcheddu, **J. Org. Chem**. **66**,7907-09 (2001).
23. L. De Luca, G. Giacomelli and A. Porcheddu, **Org. Lett. 4,** 553-5 (2002).
24. B. Karimi, H. Hazarkhani and D. Zareyee, **Synthesis** 2513-16 (2002).
25. B. Akhlaghinia, M. Asadi, E. Safaei and M. Heydarpoor. **J. Porphyrins and Phthalocyanies, 8**, 1285 -88 (2004).
26. B. Akhlaghinia, M. Asadi, E. Safaei and M. Heydarpoor, **Phosphorus, Sulfur and Silicon and the Related Elements 179**, 2099-2104 (2004).
27. B. Akhlaghinia and S. Tavakoli, **Synthesis** 1775-78 (2005).
28. B. Akhlaghinia and E. Roohi, **Lett. Org. Chem**. **2**, 725-730 (2005).
29. B. Akhlaghinia and E. Roohi, **Lett. Org. Chem**. **3**, 220-224 (2006).