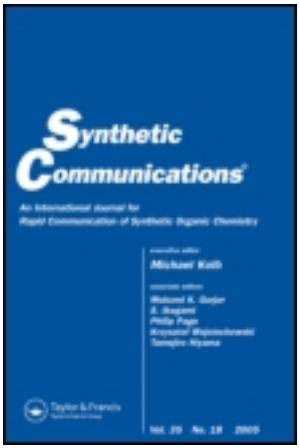

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Published online: 12 Jan 2011.

To cite this article: S. C. Puri , G. Handa , K. L. Dhar , O. P. Suri & G. N. Qazi (2004) Aminoalkylation of 10-Hydroxycamptothecin Using Methylene Chloride Under Solid-Liquid Phase Transfer Catalysis: A New Approach for the Preparation of Topotecan, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 34:15, 2857-2862, DOI: 10.1081/SCC-200026247

To link to this article: http://dx.doi.org/10.1081/SCC-200026247

SYNTHETIC COMMUNICATIONS®
Vol. 34, No. 15, pp. 2857–2862, 2004

Aminoalkylation of 10-Hydroxycamptothecin Using Methylene Chloride Under Solid–Liquid Phase Transfer Catalysis: A New Approach for the Preparation of Topotecan[#]

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ABSTRACT

The use of dichloromethane as a reagent, for the preparation of Topotecan {(4*S*)-10-(dimethylamino)methyl-4-ethyl-4,9-dihydroxy-1-H-pyrano[3′,4′:6,7]indolizino-[1,2-b]quinoline-3,14(4H,12H)dione} from 10-hydroxy-camptothecin under solid–liquid phase transfer catalysis,

[#]US Patent no. 6,660,861 December 9, 2003.

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DOI: 10.1081/SCC-200026247 0039-7911 (Print); 1532-2432 (Online)

which behaves both as a solvent and a reagent serving as for C-1 unit source for amino-alkylation of 10-hydroxy-(4*S*)-camptothecin.

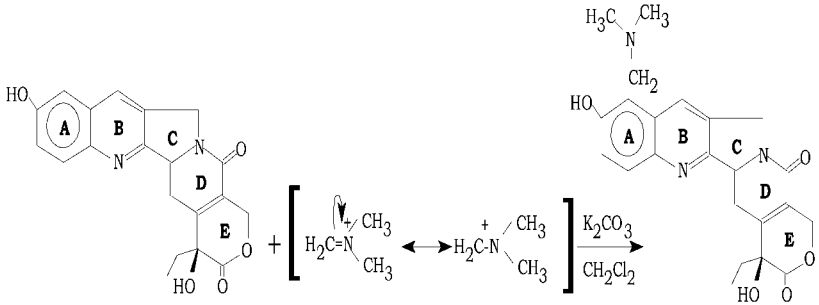
Key Words: Anticancer drugs; 10-Hydroxy-camptothecin; Mannich reaction; Methylene chloride; Topotecan.

INTRODUCTION

Topotecan 9-[(dimethylamino)methyl]-10-hydroxy-(4*S*)-camptothecin [**I**] (TPT) which is of the chemical structure (Fig. 1), is under clinical trials and its chemotherapeutic efficacy appears to be very promising.[1] Topotecan is one of the new class agents that target topoisomerase-I and stabilize the DNA–topoisomerase-I complex, ultimately resulting in the cell death. The rationale for the use of Topotecan in chronic lymphocytic leukemia (CLL) is based on the finding that Top-I levels are elevated in the lymphocytes of patients with this disease.[2]

FDA has approved Topotecan for the treatment of advanced ovarian cancers, having developed resistance to other chemotherapeutic agents, which worked as well or better than taxol in clinical trials.

The present report provides an improved process for the preparation of TPT from 10-hydroxy-(4*S*)-camptothecin [**II**] (HCPT)[3] which comprises of ortho-regioselective aminomethylation of HCPT using methylene chloride; which behaves both as a solvent and a reactant with dimethylamine under solid–liquid phase transfer catalysis. HCPT dissolved in an organic solvent and stirred at room temperature in the suspension of a solid base (potassium carbonate) and dimethylamine for the required time, then filtered and solid extracted with ethyl acetate (20 mL). The solvent was evaporated in vacuo



HCPT [II] **TPT [I]**

Figure 1. Aminoalkylation of 10-hydroxy-(4*S*)-camptothecin.

giving a residue which was purified by known methods and characterized by physico-chemical techniques.

Methylene chloride was used for aminoalkylation of 10-HCPT to TPT. Methylene chloride[4] has a double role to play where it can behave both as a solvent and a reactant for rapid reaction with dimethylamine to form Mannich adduct at atmospheric pressure. Methylene chloride and secondary amine react rapidly at room temperature and atmospheric pressure in basic conditions to form aminals (methylene-*bis*amines) as intermediates.

Our approach to the preformed methylene iminium salts (aminals), which are better electrophiles to extend the reaction to complex and relatively inert molecules, appears first of its kind. To the best of our knowledge, none of Mannich products has been obtained at atmospheric pressure, even after extended reaction time.

Solid–liquid transfer phase catalysis[5] is a straightforward route to the desired products since use of preformed-iminium salts (Mannich reagents) generally does not provide solution for aminoalkylation of indole, quinoline, and isoquinoline alkaloids.[6,7] In the present approach high reactivity coupled with minimized polyalkylation of comparatively inert substrates has been attained. In addition the yields of the desired product are substantially reduced in the absence of base which also helps in isolation of crude products by simple filtration.

Anhydrous K_2CO_3, a solid base, was used as a catalytic support. It was also observed that it is not necessary to work in anhydrous conditions. Other solid bases such as sodium carbonate, lithium carbonate, and potassium carbonate sesquihydrate have also been tried but the best results were obtained with potassium carbonate (Table 1).

The methodology provides superior yields and faster reaction under milder conditions with less undesired products for aminomethylation of complex molecules. The conventional Mannich procedure relies on the generation of aminomethyl species through equilibria involving an amine and formaldehyde which are only suitable for aminomethylation of electron-rich aromatic species and has limited scope when extended to less reactive substrates which are inert to classical Mannich conditions.[4,8]

Table 1. Aminomethylation of 10-hydroxy-(4*S*)-camptothecin (HCPT).

S. no.	Solvent	Base (15 mmol)	Yield[a] (%)
1	Dichloromethane	K_2CO_3 (2.17 g)	65
2	Dibromomethane	K_2CO_3 (2.17 g)	60
3	Diiodomethane	K_2CO_3 (2.17 g)	34
4	Dichloromethane	*K_2CO_3, 1.5 H_2O (2.17 g)	60
5	Dichloromethane	Na_2CO_3 (1.44 g)	34
6	Dichloromethane	K_2CO_3 (2.17 g)	54
7	Dichloromethane	K_2CO_3 (2.17 g)	31
8	Dichloromethane/toluene	Li_2CO_3 (2.17 g)	41
9	Dichloromethane/DMF	K_2CO_3 (2.17 g)	14

Note: For each reaction HCPT (0.364 g, 0.01 mmol), dimethylamine 12 mL, dihalomethane 50 mL and base 0.15 mmol *except K_2CO_3, 1.5 H_2O 20 mmol for 5 hr at room temperature.

[a]Yields are not theoretical but based on HPLC determination.

Though the yields, while using dibromo and diiodomethane, were slightly lower, keeping in view the cost and the ease with which the reagents are required to be handled, methylene chloride appears to be the best.

EXPERIMENTAL

General

All the reagents were purchased from E. Merck and Ranbaxy and used without further purification. The solvents used were of commercial grade and were doubly distilled. The yields reported are not theoretical but are on the basis of HPLC determination. HPLC was recorded on Gilson HPLC with 306 pump and 10 SC PUMP head 306 manometric module, 115 UV detector set at 254 nm, Rheodyne injector 7725i with 50 μL sample loop was used with Merck Lichrosphere 5 μm particle size, 4 mm × 100 mm size RP-C18 column. The isocratic mobile phase used was 60% methanol/water. IR spectra were recorded on a PC-16-FT Perkin Elmer Spectrophotometer and UV on Perkin Elmer UV/VIS spectrophotometer Lambda 3β. ^{1}H NMR were recorded on INOVA-600 "eden" using $CDCl_3$ as solvents. $SiMe_4$ was used as internal standard. Various splitting patterns were designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; bs,

broad signal. Chemical shifts were expressed in units (ppm) and coupling constants in Hz.

General Procedure for Aminomethylation of 10-Hydroxy-(4*S*)-camptothecin to 9-[(Dimethylamino)methyl]-0-hydroxy(4*S*)-camptothecin (Topotecan)

A solution of HCPT (0.364 g 0.01 mmoL) and 40% aqueous dimethylamine (12 mL) was added to methylene chloride (50 mL) containing anhydrous potassium carbonate (2.17 g, 15 mmoL) in suspension. The reaction mixture was stirred at room temperature for 5 hr, then filtered and solid extracted with ethylacetate (20 mL). The solvent evaporated in vacuo giving a residue. The residue was triturated with 0.5% aqueous HCl (50 mL) to dissolve the water-soluble adduct. Aqueous solution was partitioned with petroleum ether (3 mL × 50 mL), followed by ethylacetate (3 mL × 50 mL). The aqueous layer on lyophilization afforded white powder identified as Topotecan hydrochloride (yield: 0.236 g, 65%) on the bases of the following:

$C_{23}H_{23}N_3O_5$ as HCl m.p. 215° (dec.) (m/z 421.44); IR (KBr) 3400, 2960, 1740, 1650, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) as its acetate 1.04 (t, 3, $J = 7$ Hz, C-18), 1.96 (q, 2, $J = 7$ Hz, C-19), 2.01 (s, 3, CH_3CO_2), 2.50 (s, 6, $(CH_3)_2NH$), 4.20 (s, 2, $ArCH_2N$), 5.28 (d, 1, $J = 19$ Hz, C-17), 5.29 (s, 2, C-5), 5.50 (d, 1, $J = 10$ Hz, C-17), 7.42 (d, $J = 9$ Hz, C-11), 7.67 (s, 1, C-14), 8.05 (d, $J = 9$ Hz, C-12), 8.51 (s, C-7).

ACKNOWLEDGMENTS

We thank Dr. M. C. Wani of Research Triangle Institute, Research Triangle park, North Carolina 277709, USA for providing reference standard of HCPT and Prof. Dr. M. Spiteller, Managing Director, INFU University of Dortmund, Dortmund, Germany for high resolution NMR.

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Received in India April 5, 2004