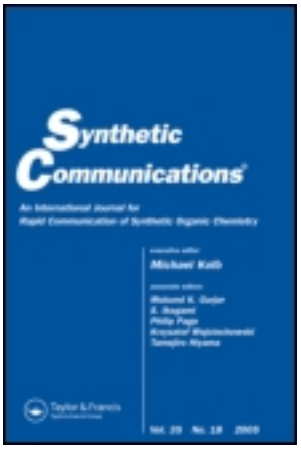

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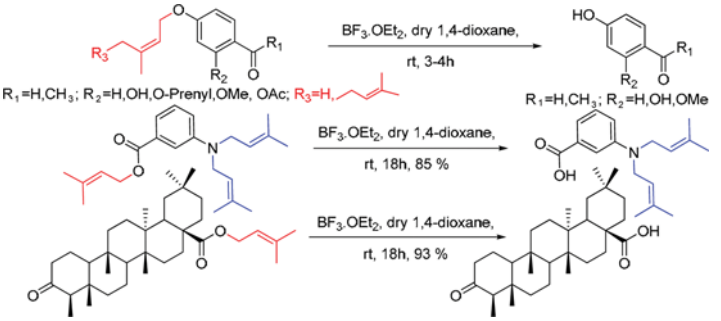
GRAPHICAL ABSTRACT



Abstract *An efficient, simple, and practical method has been developed for the deprotection of prenyl, geranyl, and phytyl ethers and esters of aromatic and aliphatic compounds using borontrifluoride–etherate ($BF_3 \cdot OEt_2$) at room temperature in good to excellent yields for the first time.*

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Keywords $BF_3 \cdot OEt_2$; deprotection; geranylether; prenylester; prenylether

INTRODUCTION

The proper introduction and removal of protecting groups are two of the most important and widely carried out synthetic transformations in preparative organic chemistry,[1] in particular, in the highly selective construction of complex polyfunctional molecules and in the synthesis of natural products such as alkaloids,

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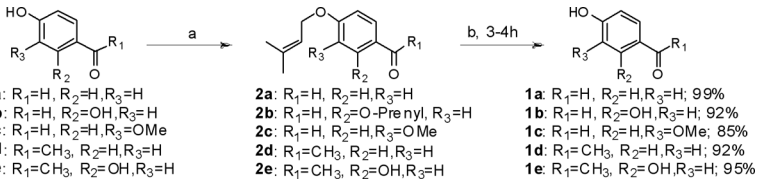
macrolides, polyether antibiotics, and prostaglandins. Regularly the problem arises that a given functional group has to be protected or deprotected selectively under the mildest conditions and in the presence of functionalities of similar reactivity as well as in the presence of structures sensitive to acids and bases. Organic chemists have to some extent responded to these challenges to achieve selectivity in organic synthesis.

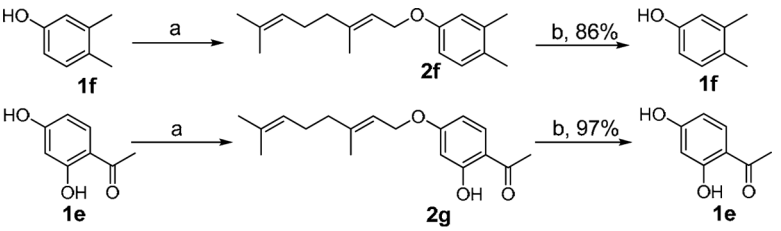
During our drug discovery program on the synthesis of bioactive prenylated chalcones,[2–6] we observed a facile prenyl group deprotection of acetophenones under the influence of $BF_3 \cdot OEt_2$. Deprotection attempts were also successful on geranyl and phytylated aromatic ethers using $BF_3 \cdot OEt_2$, which prompted us to carry out further work on this reagent. Our literature survey revealed that several alkyl groups (methyl,[7–10] ethyl,[11] t-butyl[12,13]) have been used to protect the phenolic compounds; however, they need drastic conditions for protection as well as deprotection, which also affect other functional groups. Newer protecting groups such as methoxymethylchloride (MOMCl)[14–18] methoxyethoxymethylchloride (MEMCl),[19] 2-(trimethylsilyl) ethoxymethylchoride (SEMCl),[20,21] and tetrahydrophyranoether (THP ethers)[22,23] have been developed that needs milder conditions. The prenyl group has also been used for protection of alcohols and phenols;[24–34] however, the reported reagents in deprotection of the prenyl group lack selectivity in multifunctional compounds. To our knowledge, so far $BF_3 \cdot OEt_2$ has not been used for the deprotection of prenylethers. We therefore report the selective deprotection of prenylethers of aromatic compounds using $BF_3 \cdot OEt_2$ for the first time. In addition, we also demonstrate the utility of geranyl and phytyl groups as protecting groups and deprotection by $BF_3 \cdot OEt_2$.

Initially phenolic hydroxyls of few aldehydes (**1a**–**1c**) and acetophenones (**1d**–**1e**) were protected using prenylbromide in the presence of K_2CO_3 in dry acetone to provide the respective prenylethers (**2a**–**2e**). The resultant prenyl ethers were treated with a stochiometric amount of $BF_3 \cdot OEt_2$ in dry 1,4-dioxane, which cleanly provided the respective deprenylated (**1a**–**1e**) compounds in good to excellent yields (Scheme 1). It is noteworthy to mention here that the $BF_3 \cdot OEt_2$ did not affect the O-methyl ether of **1c**.

Encouraged by these results, we then focused on increasing the chain length of the alkenyl group (Scheme 2). O-Geranylated compounds were prepared from 3,4-dimethylphenol (**1f**) and 2,4-dihydroxyacetophenone (**1e**) using the same protocol as described previously and subjected to degeranylation using $BF_3 \cdot OEt_2$, which again deprotected the geranyl group to give **1f** and **1e** in excellent yields.



Scheme 1. Protection of aromatic aldehydes and ketones by prenyl bromide and deprotection by $BF_3 \cdot OEt_2$. Reagents and conditions: (a) K_2CO_3, dry acetone, prenyl bromide, rt, 5 h; (b) $BF_3 \cdot OEt_2$, dry 1,4-dioxane, rt.

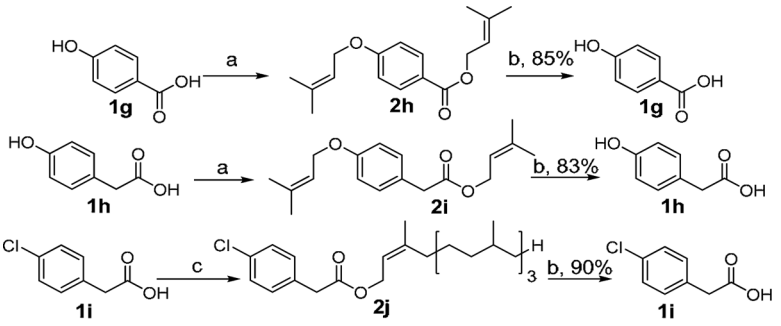


Scheme 2. Protection of phenol and polyhydroxyacetophenone by geranyl bromide and deprotection by $BF_3 \cdot OEt_2$. Reagents and conditions: (a) K_2CO_3, dry acetone, prenyl bromide, rt, 5 h; (b) $BF_3 \cdot Et_2O$, dry 1,4-dioxane, rt, 3 h.

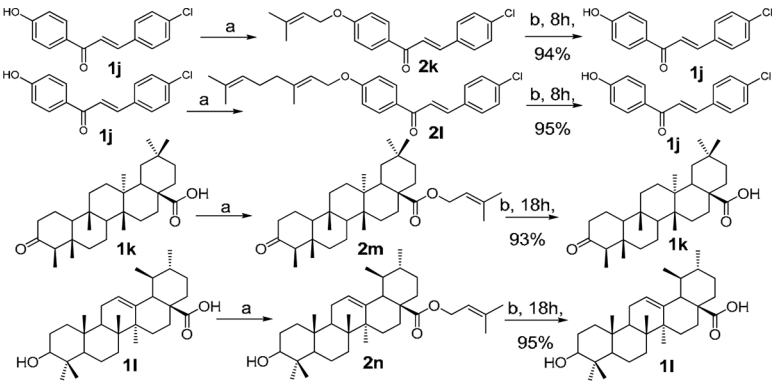
We further explored $BF_3 \cdot OEt_2$ for deprotection of aromatic and aliphatic esters (Scheme 3). p-Hydroxybenzoic acid (**1g**) and p-hydroxyphenylacetic acid (**1h**) were prenylated to provide **2h** and **2i**, which contain ester and ether functionality, and subjected to a reaction with $BF_3 \cdot OEt_2$, which deprotected the both prenyl groups (ether and ester) of **2h** and **2i** in good yields. Similar results were obtained with phytyl ester **2j** upon reaction with $BF_3 \cdot OEt_2$ to give **1i**.

To demonstrate the application of this methodology in the natural product chemical transformations, chalcone **1j** was protected with prenyl and geranyl groups to give **2k** and **2l** respectively and subsequently reacted with $BF_3 \cdot OEt_2$, which provided the dealkenylated chalcone **1j**. Prenyl esters (**2m** and **2n**) of two terpenes such as 3-oxo-freideline-carboxilic acid (**1k**) and ursolic acid (**1l**) were prepared and subjected to deprenylation reaction using $BF_3 \cdot OEt_2$ to give respective acids (Scheme 4) in excellent yields.

Allyl derivative of p-hydroxyacetophenone (**2o**), N-prenylated nitroaniline (**2p**), and O-butyl derivative of **1g** were prepared using allylbromide, prenylbromide, and n-butylbromide, respectively; however, $BF_3 \cdot OEt_2$ did not deprotect any of these three compounds (Scheme 5), which clearly indicated the selectivity of $BF_3 \cdot OEt_2$ toward prenyl and geranyl groups. To further study the selectivity toward deprotection of N-alkenyl and O-alkenyl groups, **2r** was prepared from **1n**, and deprenylation



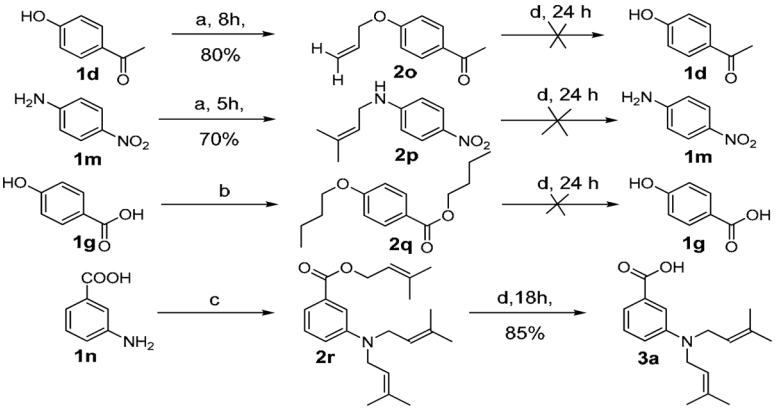
Scheme 3. Synthesis of esters by prenyl bromide and phytol and their deprotection by $BF_3 \cdot OEt_2$. Reagents and conditions: (a) K_2CO_3, dry acetone, prenyl bromide, rt, 5 h; (b) $BF_3 \cdot OEt_2$, dry 1,4-dioxane, rt, 18 h; (c) DCC, DMAP, dichloromethane, phytol, rt, 4 h.



Scheme 4. Etherification and esterification of a few natural products by prenyl bromide and geranylbromide and deprotection by $BF_3 \cdot OEt_2$. Reagents and conditions: (a) K_2CO_3, dry acetone, alkenyl bromide, rt; (b) $BF_3 \cdot Et_2O$, dry 1,4-dioxane, rt.

reactions led to selective deprotection of ester group only to give N,N-diprenylbenzoic acid (**3a**).

The reaction mechanism in the deprotection of prenyl, geranyl, and phytyl group appears (Fig. 1) to be a depolarization of the C-O bond by $BF_3 \cdot OEt_2$, leading to breaking of the C-O bond and subsequent removal of allylic hydrogen from methyl group to give the stable diene. The formation of isoprene (diene) was confirmed by thin-layer chromatography (TLC) and gas chromatography (GC) with an authentic sample of isoprene during the deprotection reaction on **2d** to **1d**. In the case of O-allylated acetophenone (**2o**), formation of stable diene is not possible, and hence failure of deprotection to provide **1d**, which supports our proposed reaction mechanism. Further studies, however, are required to confirm the exact reaction mechanism.



Scheme 5. Synthesis of O-allylated, N-prenylated and O-alkylated aromatic compounds and attempt to deprotect O-allyl, N-prenyl, and O-alkyl groups by $BF_3 \cdot OEt_2$. Reagents and conditions: (a) K_2CO_3, dry acetone, allyl bromide, rt; (b) K_2CO_3, dry acetone, n-butyl bromide, rt, 12 h; (c) K_2CO_3, dry acetone, prenyl bromide, rt, 5 h, 80%; (d) $BF_3 \cdot Et_2O$, dry 1,4-dioxane, rt.

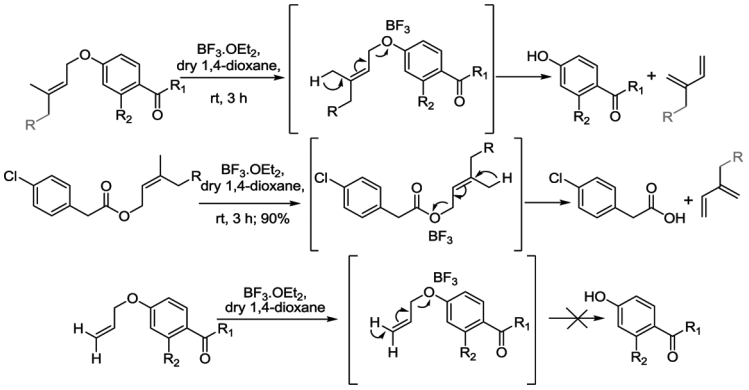


Figure 1. Possible reaction mechanism in the deprotection of aromatic ethers and esters by $BF_3 \cdot OEt_2$.

In summary we developed highly efficient method for selectively deprotecting the prenyl, geranyl, and phytyl ethers and esters of aromatic and aliphatic compounds using $BF_3 \cdot OEt_2$ for the first time in good to excellent yields. We also demonstrated geranyl and phytyl groups as protecting groups and deprotection by $BF_3 \cdot OEt_2$ for the first time. Our method has several advantages such as easy deprotection, simple procedure, good yields, and tolerance to other functional groups such as aromatic alkyl ethers, alkyl esters, amides, alkyl amines, and alkenylamines. This method can also be very useful in the synthesis and chemical transformation of natural products of biological importance.

EXPERIMENTAL

^{1}H NMR and ^{13}C NMR spectra were run on Bruker Advance DPX 200- and 300-MHz spectrometers in $CDCl_3$, and tetramethylsilane (TMS) was used as the internal standard. Electrospray ionization (ESI)–mass spectra (MS) were recorded on a Jeol S × 102 = DA-6000. Silica gel (60–120 mesh) was used as stationary phase to isolate the compounds.

Representative Procedure for Preparation of Prenylated, Geranylated Alcohol, Phenols, Esters, and Amines

To a stirred solution of alcohol, phenol or amine (1 equivalent) in dry acetone and dry K_2CO_3 was added prenyl or geranyl bromide (1 to 2 equivalent) at room temperature. The resultant solution was stirred for 5–6 h. The reaction mixture was then filtered through sintered funnel to remove K_2CO_3 and the filtrate was evaporated under reduced pressure. The crude mixture was purified by silica gel column chromatography using hexane-ethylacetate (99:1) for **2a, 2b, 2d, 2f, 2m**, hexane-ethylacetate (98:2) for **2e, 2g, 2h, 2i, 2n, 2r**, hexane-ethylacetate (97:3) for **2o, 2p**, hexane-ethylacetate (96:4) for **2k, 2l** and hexane-ethylacetate (94:6) for **2c** as a mobile phase to afford protected compound.

Representative Procedure for Preparation of Phytylated Esters

The solution of carboxylic acid (1 equivalent) in DCM was added DCC (1.5 equivalents) and DMAP (catalytic amount). Phytol (1.2 equivalents) was then added to the reaction mixture. Whole solution was stirred for 4 h. The reaction mixture was then filtered off the solid part and filtrate was concentrated under reduced pressure. The crude was purified by column chromatography using hexane-ethylacetate (98:2) mobile phase to afford the pure ester **2j**.

Representative Procedure for the Deprotection of Prenylated, Geranylated, or Phytylated Ethers and Esters

BF_3-OEt_2 (1.5 to 2 equivalents) gradually was added to a stirred solution of prenylated ether or ester (1 equivalent) in 1,4-dioxane at room temperature. The resultant solution was stirred for 3–6 h. The reaction mixture was then diluted with ethyl acetate and washed with water three to four times to decompose the BF_3-OEt_2 complexes. The organic solution obtained after extraction was dried over anhydrous Na_2SO_4 and filtered, and the solvent was evaporated under reduced pressure. The crude mixture was purified by silica gel column chromatography using hexane–ethylacetate (97:3) for **1k**, hexane–ethylacetate (96:4) for **1l**, hexane–ethylacetate (95:5) for **1a, 1b, 1d, 1e, 2f, and 1i**, hexane–ethylacetate (94:6) for **3a**, and hexane–ethylacetate (90:10) for **1c, 1g, 1h,** and **1j** as a mobile phase to afford the deprotected compound.

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REFERENCES

1. (a) Green, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis; 2nd ed.*; John Wiley: New York, 1991; (b) Kocieneski, P. J. *Protecting Groups*; Thieme: Stuttgart, 1994.
2. Narender, T.; Reddy, K. P. A simple and highly efficient method for the synthesis of chalcones by using borontrifluoride–etherate. *Tetrahedron Lett.* **2007**, *48*, 3177.
3. Narender, T.; Reddy, K. P. BF_3–Et_2O-mediated biogenetic-type synthesis of chromanochalcones from prenylated chalcones via a regioselective cyclization reaction. *Tetrahedron Lett.* **2007**, *48*, 7628.
4. Narender, T.; Reddy, K. P. Shweta BF_3-Et_2O-mediated one-pot synthesis of acetylchromans from polyhydroxyacetophenones and isoprene/allyl alcohol. *Synth. Commun.* **2009**, *39*, 384.
5. Narender, T.; Reddy, K. P.; Shweta; Mishra, D. K.; Srivastava, K.; Puri, S. K. Total synthesis of munchiwarin, a triprenylated chalcone from *Crotalaria medicagenia*. *Org. Lett.* **2007**, *9*, 5369.
6. Narender, T.; Tanvir, K.; Nishi Goel, N.; Gupta, S. Synthesis of chromenochalcones and evaluation of their in vitro antileishmanial activity. *Biorg. Med. Chem.* **2005**, *13*, 6543.

7. Sinhababu, A. K.; Kawase, M.; Borchardt, R. T. t-Butyldimethylsilyl ethers of phenols: Their one-step conversion to benzyl or methyl ethers and utility in regioselective o-lithiation. *Tetrahedon Lett.* **1987**, *28*, 4139.
8. Barcelo, G.; Grenouillat, D.; Senet, J. P.; Sennyey, G. Pentaalkylguanidines as etherification and esterification catalysts. *Tetrahedron* **1990**, *46*, 1839.
9. Jung, M. E.; Lyster, M. A. Quantitative dealkylation of alkyl ethers via treatment with trimethylsilyl iodide: A new method for ether hydrolysis. *J. Org. Chem.* **1977**, *42*, 3761.
10. Ohsawa, T.; Hatano, K.; Kayoh, K.; Kotabe, J.; Oishi, T. Quantitative dealkylation of alkyl ethers via treatment with trimethylsilyl iodide: A new method for ether hydrolysis. *Tetrahedron Lett.* **1992**, *33*, 5555.
11. Rigby, J. H.; Mateo, M. E. Total synthesis of (+)-narciclasine. *J. Am. Chem. Soc.* **1997**, *119*, 12655.
12. Holcombe, J. L.; Livinghouse, J. S. A new and specific method for the protection of phenols as the corresponding *tert*-butyl ethers. *J. Org. Chem.* **1986**, *51*, 111.
13. Masada, H.; Oishi, Y. A new synthesis of aryl *t*-butyl ethers. *Chem. Lett.* **1978**, *1*, 57.
14. Van Heerden, F. R.; Van Zyl, J. J.; Rall, G. J. H.; Brandt, E. V.; Roux, D. G. Phase-transfer catalysis: A general method of methoxymethylation of the hydroxyl function. *Tetrahedron Lett.* **1978**, *19*, 661.
15. Yardley, J. P.; Fletcher, H. Introduction of the methoxymethyl ether protecting group. *Synthesis* **1976**, 244.
16. Rahman, M. A. A.; Elliott, H. W.; Binks, R.; Kung, W.; Rapoport, H. Synthesis and pharmacology of 6-methylenedihydrodesoxymorphine. *J. Med. Chem.* **1996**, *9*, 1.
17. Williams, D. R.; Barner, B. A.; Nishitani, K.; Phillips, J. G. Total synthesis of milbemycin. *J. Am. Chem. Soc.* **1982**, *104*, 4708.
18. Falck, J. R.; Reddy, K. K.; Chandrasekhar, S. Synthesis and structure revision of the *myo*-inositol monophosphatase inhibitor L-671,776. *Tetrahedron Lett.* **1997**, *38*, 1607.
19. Corey, E. J.; Danheiser, R. L.; Chandrasekaran, S.; Siret, P.; Keck, G. E.; Gras, J. L. Stereospecific total synthesis of gibberellic acid: A key tricyclic intermediate. *J. Am. Chem. Soc.* **1978**, *100*, 8031.
20. Leboff, A.; Carbonnelle, A. C.; Alazard, J. P.; Thal, C.; Kende, A. S. Intramolecular radical coupling of a phenolic enolate: Oxidative fragmentation of the spirodiketone intermediate. *Tetrahedron Lett.* **1987**, *28*, 4163.
21. Saimoto, H.; Kusano, Y.; Hiyama, T. A mild procedure for hydrolysis of alkoxymethyl aryl ethers to give hydroxyarenes: A rational synthesis of ascofuranone. *Tetrahedron Lett.* **1986**, *27*, 1607.
22. Cruz-Almanza, R.; Perez-Floress, F. J.; Avila, M. Deprotection of tetrahydropyranyl ethers with a Mexican bentonite: Synthesis of farnesylhydroquinone. *Synth. Commun.* **1990**, *20*, 1125.
23. Ballini, R.; Bigi, F.; Carloni, S.; Maggi, R.; Sartori, G. Solvent-free tetrahydropyranylation of phenols and alcohols over zeolites HSZ as reusable catalysts. *Tetrahedron Lett.* **1997**, *38*, 4169.
24. Guibe, F. Allylic protecting groups and their use in a complex environment, part I: Allylic protection of alcohols. *Tetrahedron* **1997**, *53*, 13509.
25. Sharma, G. V. M.; Ilangovan, A.; Mahalingam, A. K. A mild and highly selective deprotective method of prenyl ethers using ytterbium triflate. *J. Org. Chem.* **1998**, *63*, 9103.
26. Babu, K. S.; Raju, B. C.; Srinivas, P. V.; Rao, J. M. Highly efficient and chemoselective cleavage of prenyl ethers using $ZrCl_4/NaBH_4$. *Tetrahedron Lett.* **2003**, *44*, 2525.
27. Babu, K. S.; Raju, B. C.; Srinivas, P. V.; Rao, A. S.; Kumar, S. P.; Rao, J. M. A simple, effective, and highly selective cleavage of 3-methylbut-2-enyl (prenyl) ethers using p-toluenesulfonic acid. *Chem. Lett.* **2003**, *32*, 704–705.

28. Sharma, G. V. M.; Govardhan Reddy, C.; Radhakrishna, P. A simple and efficient protocol for the deprenylation of ethers and esters catalysed by zirconium(IV) chloride–sodium iodide. *Synlett* **2003**, 1728.
29. Tsuritani, T.; Shinokubo, H.; Oshima, K. Highly selective cleavage of prenyl ethers by means of a $TiCl_4$-*n*-Bu_4NI mixed reagent. *Tetrahedron Lett.* **1999**, *40*, 8121.
30. Vatele, J. M. Iodine in dichloromethane—A simple method for selective cleavage of prenyl ethers. *Synlett* **2001**, 1989.
31. Vatele, J. M. An efficient and chemoselective cleavage of prenyl ethers with DDQ. *Synlett* **2002**, 507.
32. Cossy, J.; Albouy, A.; Scheloske, M.; Pardo, G. A very useful and mild method for the protection and deprotection of carboxylic acids. *Tetrahedron Lett.* **1994**, *35*, 1539.
33. Yadav, J. S.; Subba Reddy, B. V.; Rao, C. V.; Chand, P. K.; Prasad, A. R. A facile and selective cleavage of prenyl esters catalyzed by $CeCl_3 \cdot 7H_2O$-NaI. *Synlett* **2002**, 137.
34. Ramesh, C.; Mahender, G.; Ravindranath, N.; Das, B. A simple, mild and efficient procedure for selective cleavage of prenyl esters using silica-supported sodium hydrogen sulphate as a heterogenous catalyst. *Tetrahedron Lett.* **2003**, *44*, 1465.