Pergamon

Tetrahedron Letters 43 (2002) 8603–8606

TETRAHEDRON
LETTERS

An efficient approach towards syntheses of ethers and esters using CsF–Celite as a solid base

Syed Tasadaque A. Shah,[a] Khalid M. Khan,[b] Angelica M. Heinrich,[a] M. Iqbal Choudhary[b] and W. Voelter[a,*]

[a]*Abteilung für Physikalische Biochemie des Physiologisch-chemischen Instituts der Universität Tübingen, Hoppe-Seyler Straße 4, D-72076 Tübingen, Germany*

[b]*HEJ Research Institute of Chemistry, International Center for Chemical Sciences, University of Karachi, Karachi 75270, Pakistan*

Received 17 July 2002; accepted 6 September 2002

Abstract—The coupling reactions of a number of alcohols and phenols with alkyl, acyl or benzoyl halides in acetonitrile with cesium fluoride–Celite are described. It has been found that CsF–Celite combinations provide an efficient, convenient and practical method for syntheses of both, ethers and esters. © 2002 Elsevier Science Ltd. All rights reserved.

Hydroxyl groups are present in a number of compounds of biological and synthetic interest, including nucleosides, carbohydrates, steroids and alkaloids, etc. During oxidation, acylation, halogenation with phosphorus or hydrogen halides, or dehydration reactions of these compounds, a hydroxyl group must be protected. Ethers and esters are among the most used protective groups in organic synthesis which were formed and removed under a wide variety of conditions.[1] However, these methods suffer serious limitations, when the substrates have acid or base labile moieties in their skeletons.

Yin et al.,[2] reported protection of hydroxyl groups as ethers using allyl bromide- and potassium fluoride-impregnated alumina. Hijfte and Little reported[3] *O*-alkylation of primary alcohols with benzyl bromide and Ag_2O in DMF, however, use of benzyl and benzoyl halides for the protection of primary and secondary alcohols is more often used in carbohydrate synthesis.[4] Although acylation of alcohols and phenols is routinely carried out using acid anhydrides or acyl halides in the presence of tertiary amines such as triethylamine and pyridine.[5] Vedejs and co-workers reported tributylphosphine as a catalyst for acylation of alcohols.[6] However, there is still a demand for base catalysts to generate ethers and esters via an environmentally friendly process. We wish to report a practical and convenient method for the preparation of ethers and esters using cesium fluoride–Celite as a solid base which can overcome such types of limitations. We also demonstrate herewith the utility of CsF–Celite/CH_3CN for the syntheses of ethers and esters using the reaction conditions, presented below.

The importance of the fluoride ion as a catalyst for the promotion of various types of base-catalyzed reactions in organic synthesis has been previously recognized.[7] The work of Clark and Miller, in particular, revealed that the fluoride ion has an effect on coupling reactions because of its high capability of hydrogen-bond formation.[8] As reagents for generating the fluoride ion in these reactions, potassium, cesium and tetra-alkylammonium fluorides were generally used so far. However, it is not easy to handle these hygroscopic reagents and the reproducibility of these reactions are invariably poor. Previously, poorly hygroscopic reagent generating fluoride ions were designed by allowing cesium fluoride to be absorbed on Celite.[9] The effect of cesium fluoride–Celite might be twofold: (a) activation of the hydroxyl group by the fluoride ion, whose ionic character is increased owing to the low charge/surface

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* Corresponding authors. E-mail: tasadaque@hotmail.com; wolfgang.voelter@uni-tuebingen.de

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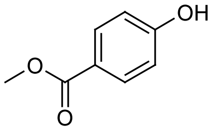
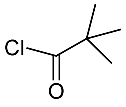
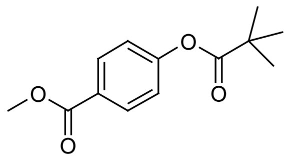
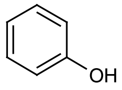
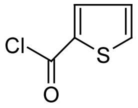
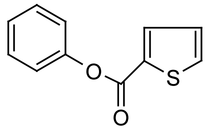
PII: S0040-4039(02)02060-9

Table 1. *O*-Acylation of hydroxyl groups using CsF–Celite

No.	Substrate	Reagent	Product	% Yield	Mp (lit.)
1	C_6H_5OH	CH_3COCl	$C_6H_5CO_2CH_3$	89[a]	Liquid[11]
2	C_6H_5OH	C_6H_5COCl	$C_6H_5CO_2C_6H_5$	88[b]	Liquid [12]
3	C_6H_5OH	$4\text{-}NO_2C_6H_4COCl$	$4\text{-}NO_2C_6H_4CO_2C_6H_5$	84[a]	128-129, (128-129)[13]
4	$C_6H_5CH_2OH$	C_6H_5COCl	$C_6H_5CH_2CO_2C_6H_5$	78[a]	Liquid[14]
5	$CH_3OC_6H_4OH$	$4\text{-}NO_2C_6H_4COCl$	$CH_3OC_6H_4CO_2C_6H_4NO_2$	76[b]	96-98, (96.5-97.5)[13]
6	$4\text{-}C_6H_5C_6H_4OH$	C_6H_5COCl	$4\text{-}C_6H_4C_6H_4CO_2C_6H_5$	63[b]	149-151, (149-150)[15]
7	$3\text{-}C_6H_5C_6H_4OH$	$CH_3O_2C(CH_2)_2COCl$	$2\text{-}C_6H_5C_6H_4CO_2(CH_2)_2CO_2CH_3$	59[b]	Liquid[16]
8	$4\text{-}C_6H_5C_6H_4OH$	CH_3COCl	$4\text{-}C_6H_5C_6H_4CO_2CH_3$	78[b]	87-88, (87-88)[17]
9				82[b]	Liquid[18]
10				73[b]	44-45, (44-45)[19]

a = room temp., b = reflux at 82 °C

area ratio of the cesium cation and (b) activation of the alkyl or acyl halide groups by a Lewis acid type effect.[10]

The reactions catalyzed by cesium fluoride–Celite are usually carried out under mild conditions with good yields and simple workup of these reactions; only filtration is required to remove the catalyst and often evaporation of the filtrate afforded pure products. Previously in a short communication,[9b] esters of acids were prepared from carboxylic acids and alkyl halides via CsF–Celite catalysis, however, this report is limited only to the formation of esters from acids, whereas they have also used the alcoholic moieties in their reactions, but they overlooked the utility of this solid base under the same reaction conditions for the protection of an alcohol as an ether or ester. We explored further utility of the CsF–Celite system as an efficient, inexpensive, non-corrosive and an environmentally friendly reagent for the protection of a hydroxy function to an ether or ester depending upon the substrate used.

Several examples of CsF–Celite-assisted couplings of aromatic hydroxyl groups with various alkyl or acyl halides, resulting in alkylation, acylation benzylation and benzoylation are presented in Tables 1 and 2.

In a typical reaction, a mixture of alcohol (1.0 mol), CsF–Celite (1.5 mol) and alkyl or acyl halide (2.0 mol) in acetonitrile is stirred at room temperature or under reflux (Scheme 1). The completion of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was filtered and the filtrate was evaporated to afford the pure product.

$$\text{ROH} + \text{R'X} \xrightarrow[\text{CH}_3\text{CN, r.t. or Reflux}]{\text{CsF-Celite}} \text{ROR'}$$

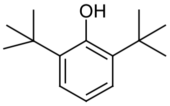
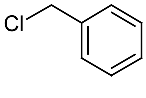
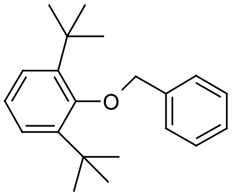
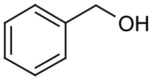
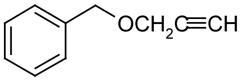
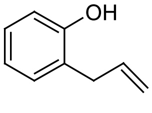
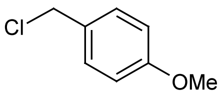
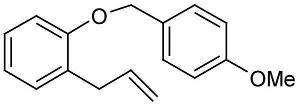
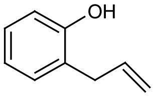
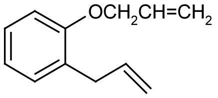
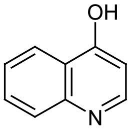
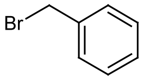
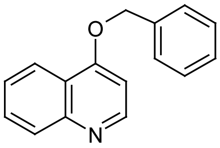
R = Phenyl or Benzyl
X = Cl, Br or I
R'= Alkyl, Acyl, Benzyl or Benzoyl

Scheme 1.

Acknowledgements

We express our gratitude to Deutscher Akademischer Austauschdienst (DAAD, Bonn, Germany) for a sandwich-type scholarship, granted to Syed Tasadaque Ali Shah and a short term scholarship, granted to Dr. Khalid Mohammed Khan.

Table 2. *O*-Alkylation of hydroxyl groups using CsF–Celite

No.	Substrate	Reagent	Product	% Yield	Mp (lit.)
1	C_6H_5OH	$C_6H_5CH_2Br$	$C_6H_5OCH_2C_6H_5$	91[a]	39-40, (39)[20]
2	C_6H_5OH	$CH_2{=}CHCH_2Br$	$C_6H_5OCH_2CH{=}CH_2$	77[b]	Liquid[21]
3	C_6H_5OH	$4\text{-}NO_2C_6H_4CH_2Cl$	$4\text{-}NO_2C_6H_4CH_2OC_6H_5$	71[b]	90-91, (91)[22]
4	$C_6H_5CH_2OH$	$4\text{-}NO_2C_6H_4CH_2Br$	$4\text{-}NO_2C_6H_4CH_2OCH_2C_6H_5$	82	Liquid[23]
5	$3,5\text{-}(CH_3O)_2C_6H_3OH$	$CNCH_2CH_2Br$	$3,5\text{-}(CH_3O)_2C_6H_3OCH_2CH_2CN$	67[b]	Liquid [24]
6	$4\text{-}C_6H_5C_6H_4OH$	$CH_3CH_2O_2CCH_2I$	$4\text{-}C_6H_5C_6H_4OCH_2CO_2CH_2CH_3$	89[b]	60-61, (60)[25]
7	$4\text{-}C_6H_5C_6H_4OH$	$C_2H_5O_2CCH{=}CHCH_2Br$	$4\text{-}C_6H_5C_6H_4OCH_2CH{=}CHCO_2C_2H_5$	64[b]	69-70
8	$2\text{-}C_6H_5C_6H_4OH$	$CH_2{=}CHCH_2Br$	$2\text{-}C_6H_5C_6H_4OCH_2CH{=}CH_2$	62[b]	Liquid[26]
9	$4\text{-}NO_2C_6H_4OH$	$4\text{-}NO_2C_6H_4CH_2Br$	$4\text{-}NO_2C_6H_4OCH_2C_6H_4NO_2\text{-}4$	85[b]	187, (187.4)[27]
10				88[b]	Liquid
11		$CH{\equiv}CCH_2Br$		60	Liquid
12				54[b]	Liquid [28]
13		$CH_2{=}CHCH_2Br$		68[b]	Liquid[29]
14				81[b]	Liquid[30]

a = room temp., b = reflux at 82 °C

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