Tetrahedron Letters, Vol. 33, No. 6, pp. 749-752, 1992
Printed in Great Britain

0040-4039/92 $3.00 + .00
Pergamon Press plc

THE STEREOCONTROLLED SYNTHESIS OF VERSATILE CARBAPENEM INTERMEDIATES USING THE BARTON O-ACYL 2-THIOPYRIDYLHYDROXAMATE FRAGMENTATION

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Abstract: The photo-initiated fragmentation of 2-azetidinone-4-carboxylic acid 2-thiopyridylhydroxamates (Barton reaction) in the presence of Michael acceptors leads to the introduction of a doubly functionalized carbon chain, useful for the elaboration of carbapenem and related β-lactam antibiotics.

The discovery of the clinically and commercially important carbapenem class of β-lactam antibiotics[1] has fostered a great deal of research activity world-wide, in the quest to produce enantiomerically pure intermediates. Specific target structures have focused on the synthesis of 3,4-*trans* substituted 2-azetidinones with appropriate levels of functionalization in order to allow further elaboration into the carbapenem molecules.[2]

In the context of an on-going program in our laboratory in the area of β-lactam antibiotics,[3] we describe herein a method for the stereocontrolled C-functionalization at C-4 of the basic 2-azetidinone subunit with or without an alkyl substituent at C-3, leading to a variety of versatile intermediates for carbapenem synthesis. The method relies on the photolytic decarboxylative fragmentation of a 2-thiopyridylhydroxamate ester (Barton reaction),[4] in the presence of a variety of Michael acceptors (Scheme 1). The reaction appears to be quite general for a number of 3-substituted 2-azetidinone-4-carboxylic acids,[2,5,6] including the one with the synthetically relevant (R)-2-hydroxyethyl side-chain.[2] The alkylated products result from the generation of an intermediate radical , and its stereoselective conjugate addition to Michael acceptors containing electron withdrawing groups[7,8] to produce 3,4-*trans* substituted 2-azetidinones.

Scheme 1

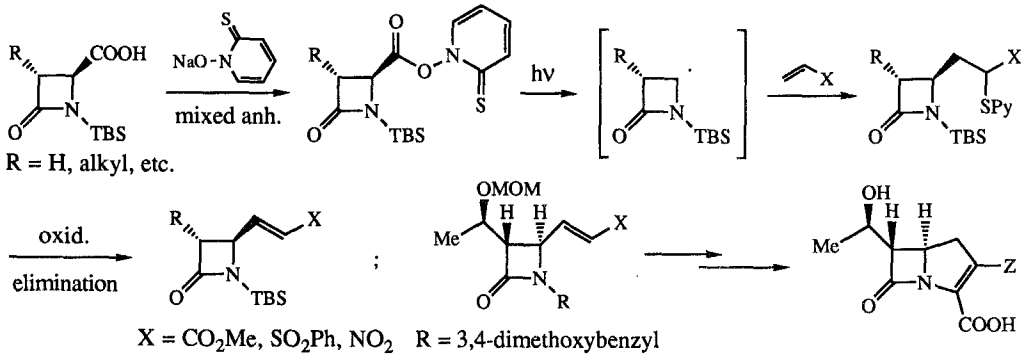
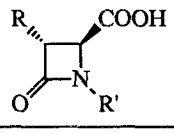
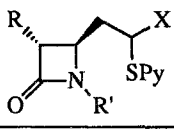
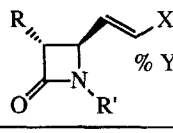
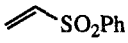
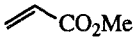
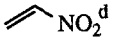
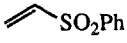
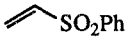
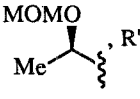
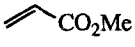
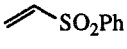
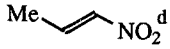
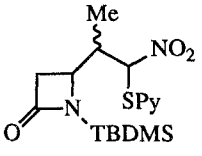
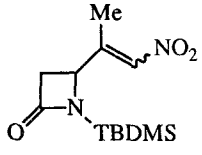
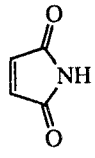
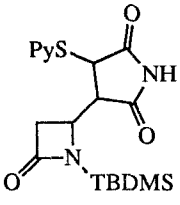
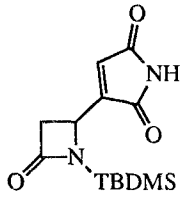


Table 1[a]

Entry		Olefin	hr.	 , %[b]	 % Yield[c]
1	R=H, R'=TBDMS		1	X=SO_2Ph,	68% 83%
2	R=H, R'=TBDMS		1	X=CO_2Me,	50% 65%
3	R=H, R'=TBDMS	 [d]	0.5	X=NO_2,	39% 80%
4	R=Me, R'=TBDMS		1	X=SO_2Ph,	77% 56%[e]
5	R=TBDMS  , R'=TBDMS		1	X=SO_2Ph,	54% 50%[f]
6	R=  , R'=DMB[g]		17	X=CO_2Me,	54% 50%[h]
7	" "		18	X=SO_2Ph,	44% 58%[i]
8	R=H, R'=TBDMS	 [d]	4	 30%	 71%
9	R=H, R'=TBDMS		2	 79%	 58%

a. For a general procedure, see text; b. Yields are for isolated products (overall from the acid via the O-acyl-2-thiopyridylhydroxamate). Novel structures gave the expected analytical and spectroscopic data; c. Two step oxidative elimination, isolated product yield; d. Reaction done in the presence of camphorsulfonic acid (2 eq.); e. $[\alpha]_D^{25}$ +10.80° (c 1.5, $CHCl_3$); f. $[\alpha]_D^{25}$ +27.97° (c 0.74, $CHCl_3$); g. DMB = 3,4-dimethoxybenzyl (see ref. 13); h. $[\alpha]_D^{25}$ -8.45° (c 1.1, $CHCl_3$); i. $[\alpha]_D^{25}$ -26.52° (c 2.3, $CHCl_3$).

An inherently versatile feature of this reaction is the formation of an alkyl chain in which the terminal carbon atom is doubly functionalized (EWG X, and S-pyridyl). Oxidative elimination of the 2-pyridylthio group[9] provides an α,β-unsaturated ester, sulphone or nitro derivative, which can be further manipulated.

Table 1 lists several examples of this reaction which is typified by the following procedure:

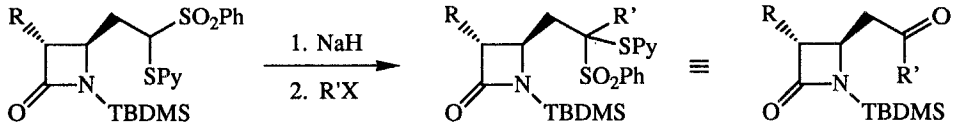
Addition: To a solution of the azetidinone carboxylic acid[5,6] (1 mmol) in anhydrous THF (7 ml) at -20°C was added N-methyl morpholine (1.1 mmol) and isobutyl chloroformate (1.1 mmol) under argon. The solution was allowed to stir at -20°C for 30 minutes, and then treated with the sodium salt of N-hydroxy-2-thiopyridone (1.2 mmol).[4] The mixture was stirred at -20°C under argon for 45 minutes in the dark, then rapidly filtered and the solids were washed with anhydrous THF (3 ml). The yellow filtrate was irradiated in the presence of the olefin (5 mmol) with a 250 W tungsten lamp under argon at ambient temperature. Concentration of the reaction mixture and purification by flash chromatography gave the adduct. In the case of nitroethylene, camphor sulphonic acid[7] (2 mmol) was added after filtration of the salts, and the filtrate was cooled again to -20°C, before adding the nitroolefin and irradiation.

Oxidative elimination. To a solution of adduct (1 mmol) in chloroform (10 ml) was added mCPBA (1 mmol). After stirring for one hour, the mixture was extracted with methylene chloride, the extracts washed ($NaHCO_3$, $KHSO_4$, brine), and processed as usual. The residue obtained after evaporation was taken up in toluene (20 ml) and the solution was heated at reflux for one hour. The solvent was then removed under reduced pressure and the residue chromatographed as usual.

Addition of the generated radical from the 2-thiopyridylhydroxamate esters to terminal olefins with conjugated electron withdrawing groups took place readily in all cases. Although in a few instances the yield for the two steps was modest due to concomitant competitive production of the 4-(2-pyridylthio)-3-azetidinone derivative, the overall process was efficient in comparison with related examples mainly from the Barton group.[4,7] The most favorable protective groups in the 2-hydroxyethyl series were found to be N-DMB and O-MOM (entries 6,7). Entry 9 shows an interesting addition to maleimide where two chromatographically separable diastereomers are formed. Oxidative elimination of each isomer led to a single 3-substituted maleimide.

In an effort to introduce a C-methyl group at the β-carbon atom of the side-chain corresponding to the 1-β-methyl carbapenems,[10] we attempted the photo-initiated fragmentation of the hydroxamate ester derived from the model 2-azetidinone-4-(S)-carboxylic acid,[5] in the presence of methyl methacrylate. Although coupling took place, the yields were modest, favoring the transfer of the 2-thiopyridyl group rather than the carbon chain of the acceptor, and stereoselectivity was low. The reluctance of β-substituted Michael acceptors to form adducts in the Barton reaction[11] as well as in other free radical reactions[8] has been previously noted. We were successful however in the case of 1-nitro-2-propene (entry 8), where the reaction was catalyzed in the presence of

Scheme 2



camphorsulfonic acid.[9] The S-pyridylthio adduct underwent oxidative elimination to give the expected β-methyl-1-nitropropenyl derivative, as a mixture of isomers.[12]

An extremely useful feature in the products obtained by this method is the ability to further functionalize the doubly substituted terminal carbon atom of the newly introduced side-chain. Thus, treatment of the sulphone adducts shown in Scheme 2, with sodium hydride followed by an alkyl halide led to the corresponding branched derivatives (Scheme 2). Undoubtedly, other radical or anionic reactions are possible at this site by virtue of the presence of an electron withdrawing group and the S-pyridylthio moiety. In the case of the phenylsulfone derivatives, the reaction products or their alkylated analogs (Scheme 2) are formally related to their carbonyl equivalents, which are strategically placed at the "C-2" position of the target carbapenem structure.

Application of the Barton photo-initiated fragmentation reaction of 2-thiopyridylhydoxamate esters to the 2-azetidinone-4-carboxylic acid derivatives offers a rapid and versatile method to functionalized carbapenem precursors.

Acknowledgements. We thank NSERCC and Lederle Laboratories (USA) for generous financial support.

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(Received in USA 14 November 1991)