Pergamon

Tetrahedron Letters, Vol. 36, No. 47, pp. 8681-8684, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)01792-5

N-Benzyltriflamide: a Generally Useful Mitsunobu Reagent for Amine Synthesis

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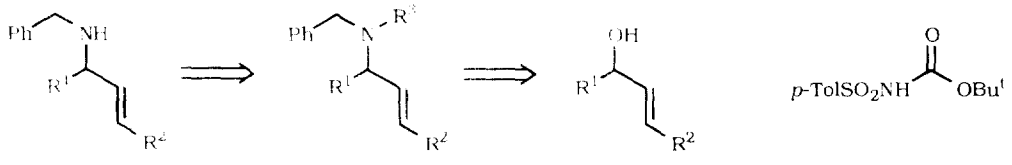
Abstract: *N-Benzyl triflamide has been found to be generally useful as a Mitsunobu nucleophile for the preparation of a range of primary and secondary benzylamines from the corresponding alcohols, using the standard reagents DEAD and triphenylphosphine*

During work aimed at extending our recent discovery of a potentially viable approach to 1,2,5-oxadiazines and thence vicinal diamines *via* a tandem *retro*-Cope elimination-Meisenheimer sequence,[1] we required a general and brief approach to a series of substituted *N*-benzyl allylamines **1** which, in principle, would be amenable to the elaboration of homochiral material. While there are many approaches available for allylamine synthesis,[2,3] these are often multistep or are specific for an individual example. Illustrative of both these features are approaches starting from α-amino-acids.[3] We were particularly attracted to the idea of using a Mitsunobu reaction[4] for our purposes for a number of reasons. Firstly, the precursors would be the corresponding allylic alcohols **3**, for which a plethora of synthetic methods are available, some of which would be suitable for the elaboration of homochiral compounds. Secondly, the nitrogen function would be introduced in one, stereochemically unambiguous step and finally, the rather difficult to handle allylamines **1** could be produced by a one-step deprotection [*i.e.* removal of 'R^3'] of the initial Mitsunobu product **2**.

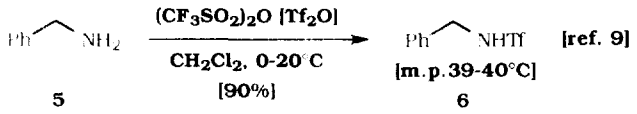


1 **2** **3** **4**

It has been amply demonstrated recently, most notably in an elegant study by Ragnarsson and his colleagues,[5] that a successful Mitsunobu displacement depends not on the nucleophilicity of the incoming nucleophile but rather on the pK_a associated with the X-H bond which must be broken as the latter participates in the key S_N2 displacement step. In general, this has to be below ~13.5 and, for displacements using amine

derivatives to be effective, necessitates the incorporation of two activating functions, one of which is usually a powerful electron withdrawing group such as a sulphonyl function [yields are generally poor with *bis*-carbamates such as Boc_2NH, pK_a 16.9].[5] Thus, we were initially successful in our aim of preparing allylamines **1** using the *N*-Boc tosylamide **4** [pK_a 8.5],[5] although this approach required difficult manipulations of the initial adducts, specifically, in our hands, a capricious reductive desulphonylation followed by removal of the Boc function and reductive *N*-benzylation and, overall, was too long and inefficient. We were therefore attracted by a recent report from the Tsunoda-Itô group who showed that the more reactive Mitsunobu reagent combination of 1,1'-(azodicarbonyl)dipiperidine (ADDP)-tributylphosphine (TBP) combined with *N*-benzyltrifluoroacetamide [pK_a 13.6] could be used to form an allylamine derivative, albeit in only 11% yield.[6] A subsequent report on the development of yet more reactive Mitsunobu reagents, especially the *N,N,N',N'*-tetramethyl azidodicarboxamide (TMAD)-TBP combination, quoted an enhanced 78% return from a Mitsunobu reaction between crotyl alcohol and *N*-benzyltrifluoroacetamide.[7] Unfortunately, these reagents are either expensive[8] or are not commercially available and their reactions with secondary allylic alcohols were poor. We reasoned that this work did, however, illustrate the important principle that the required electron withdrawing groups could be present in a single function, *i.e.* the CO and CF_3 groups in $PhCH_2NHCOCF_3$, thus giving the potential for a single step removal leading to the required *N*-benzyl allylamines **1**.[7] We reasoned that the related *N*-benzyl *triflamide* **6** with its enhanced electron withdrawing group and hence lower pK_a value, could possess the correct properties making it a superior Mitsunobu reactant. Herein, we report that this is indeed the case.

N-Benzyl triflamide **6** is a stable, crystalline solid, m.p. 39-40°C, readily prepared from benzylamine **5** and triflic anhydride [CH_2Cl_2, 0-20°C, 1h][9] and has a pK_a value of 6.8.[10] The compound has previously been used in amine synthesis, but as a nucleophile in the Gabriel synthesis.[9]

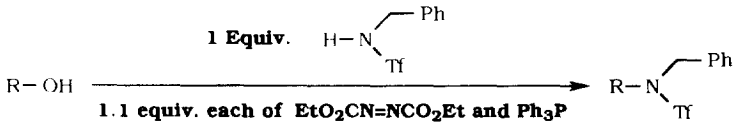


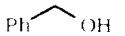
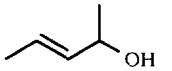
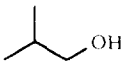
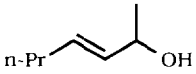
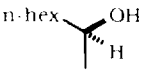
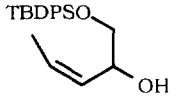
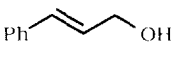
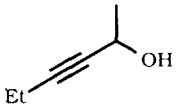
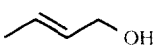
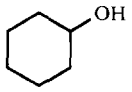
5 **6**

Our results on the Mitsunobu reactivity of the triflamide **6** are shown in Table 1, from which a number of useful observations emerge. We find that the 'standard' Mitsunobu conditions of DEAD and triphenylphosphine work well in most instances and only a slight excess of these reagents is required; tetrahydrofuran was used as the solvent throughout.[11] Both benzyl alcohol (entry 1) and a representative saturated primary alcohol (entry 2) gave excellent yields. A significant improvement relative to the use of *N*-benzyl trifluoroacetate-TMAD-TBP[7] was observed with a saturated secondary alcohol (entry 3); complete S_N2 inversion was observed when starting with homochiral material.[12] Similarly, both cinnamyl and crotyl alcohols reacted smoothly (entries 4 and 5). We were especially pleased to isolate an excellent 78% yield from our first reaction with a secondary allylic alcohol (entry 6). However, this simple example hides the fact that both S_N2 and S_N2' displacements occur with approximately equal facility with such secondary allylic alcohols, as indicated by entry 7, in which *both*

possible triflamides were isolated in very similar yields. Curiously, a similar problem did not arise with a related (Z)-allylic alcohol (entry 8) which led smoothly to a single S_N2 product. Fortunately, this severe limitation in the case of (E)-allylic alcohols was (partly) solved by the finding that a representative secondary *acetylenic* alcohol also reacted efficiently under these conditions (entry 9); no trace of an allenic product was detected by infra-red spectroscopy. One remaining limitation is that this reagent combination reacts very poorly with cyclohexanol (entry 10); the reasons for this are not clear, but other observations made recently at Nottingham indicate that such alcohols are particularly reluctant to undergo Mitsunobu displacements.[13]

Table 1. Mitsunobu Reactions of $PhCH_2NHTf/DEAD/Ph_3P$ with Representative Alcohols



Entry	Alcohol	% Yield*	Entry	Alcohol	% Yield*
1		93 [86]	6		76
2		78	7		88†
3		68 [11]	8		67
4		78	9		72
5		89 [78]	10		<5

*** Refers to isolated yields, after column chromatography, of analytically pure material. Values in parenthesis ([ ]) refer to the best reported yields obtained using $PhCH_2NHCOCF_3$-TMAD-TBP (ref. 7)**

† Obtained as an ~1:1 mixture of the S_N2 and S_N2' products

Finally, removal of the triflamide function can be carried out by reduction of the initial Mitsunobu adducts with lithium aluminium hydride in refluxing ether, as previously reported.[9] Typical isolated yields of the benzylamines were in excess of 80%. An alternative protocol[9] involving base-induced elimination of the triflamide group to give the corresponding benzaldehyde imines has not been investigated in the present study.

Acknowledgements

We are grateful to Zeneca Pharmaceuticals, the DTI and the SERC for financial support through the Asymmetric Synthesis LINK Scheme (to KEB) and The Royal Society for an award of a Leverhulme Senior Research Fellowship (to DWK).

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11. In a typical procedure, a solution of the alcohol (1 eq), *N*-benzyl triflamide (1 eq), triphenylphosphine (1.1 eq) and diethyl azodicarboxylate (DEAD) (1.1 eq) is stirred at ambient temperature in dry tetrahydrofuran (1 ml $mmol^{-1}$) for 24h then evaporated and the residue separated by column chromatography. Tributylphosphine can be used in place of triphenylphosphine; preliminary experiments indicate that such reactions are slightly faster and at least as efficient.
12. The derived chiral *N*-benzyl triflamide was compared with similarly prepared racemic material using hplc which indicated an optical purity of > 95%.
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(*Received in UK* 29 *August* 1995; *revised* 18 *September* 1995; *accepted* 22 *September* 1995)