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STEREOSPECIFIC SYNTHESIS OF SECONDARY AMINES BY THE MITSUNOBU REACTION

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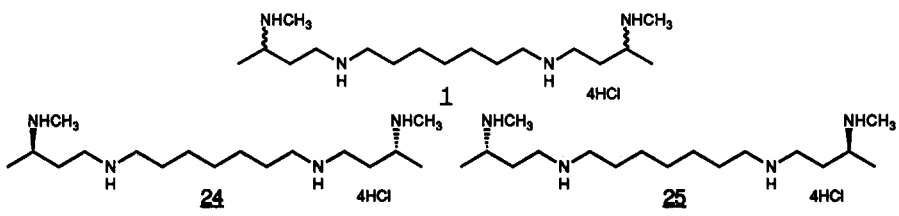
Abstract: A facile synthesis of secondary amines from alcohols is reported with N-methyltrifluoromethanesulfonamide (2) in the Mitsunobu reaction. The reaction was demonstrated to proceed with inversion of configuration and provided a convenient synthetic route to the (R,R)- and (S,S)-enantiomers (24 and 25) of the antitumor polyamine 1 by utilizing either (R)- or (S)-3-(N-methyltrifluoromethanesulfonamido)butan-1-ol (21 or 22) and 1,7-bis-(trifluoromethanesulfonamido)heptane (33). Reagents 21 and 22 were prepared from commercially available (S)- and (R)-1,3-butanediol, respectively.

Polyamines are critical in the growth of both normal and neoplastic cells and certain polyamine analogs are antitumor agents.[1,2] The biochemical importance of these compounds led to increased interest in efficient methods for their syntheses.[3-5] As part of our program of polyamine syntheses,[6] we have prepared compound 1, a potent antitumor agent. A convenient synthesis for the enantiomers of 1 was desired to ascertain the importance of the chiral centers for antitumor activity. We report a high yield method to the (R,R)- and (S,S)-enan-



tiomers (24 and 25) of 1 which utilizes N-methyltrifluoromethanesulfonamide (2) in the Mitsunobu reaction as a new method to these chiral secondary amines. In addition, we demonstrate the generality of this method for the conversion of alcohols to secondary amines.

Protected primary amines can be obtained by the Mitsunobu reaction,[7,8] and a key to the success of these reactions is the pKa of the acidic component.[9] Examination of the pKa values of N-methyltrifluoromethanesulfonamide ($TfNHCH_3$, 2; pKa 7.5)[10] and N-methyl-p-toluenesulfonamide ($TsNHCH_3$, 3; pKa 11.7)[11] suggested that both 2 and 3 might serve as useful synthons for the acidic component, providing a new stereospecific route to protected secondary amines. Reaction of $TfNHCH_3$ (2) with both primary and secondary alcohols under Mitsunobu reaction conditions gave the Tf protected secondary amines in 70-86% yield (see Table 1).[12] N-Methyl-

p-toluenesulfonamide (3) gave significantly lower yields of Ts protected secondary amines (33-53%) when reacted with the same alcohols as 2 under Mitsunobu conditions. These results are not surprising based on the pKa values of 2 and 3.[13] In the case of anilines, both Tf activation (TfNHPh, 4;[14] pKa 4.5[10]) and Ts activation (TsNHPh, 5;[15] pKa 9.3[11]) provide useful synthons for the preparation of N-substituted anilines. During the course of this work, a report describing N-alkyl-p-toluenesulfonamides in the Mitsunobu reaction appeared.[7]

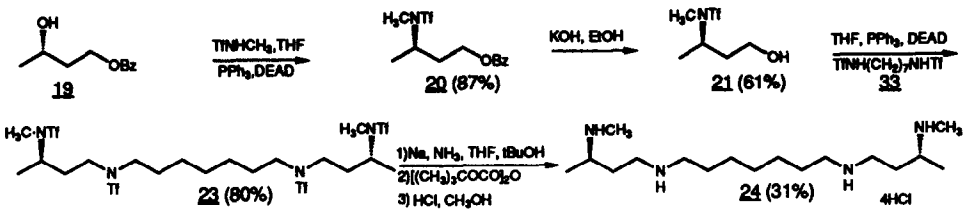
Table 1. Comparison of Tf and Ts activated amines in the Mitsunobu reaction.

PNHR + R'OH ⟶ PNRR'

PNHR	R'OH	PNRR'		YIELD,(%)	mp(bp)°C
TfNHCH$_3$ (2)	Ph⌒OH	Ph⌒NTfCH$_3$	(7)	70	225/50mm
"	OH OH	NTfCH$_3$ NTfCH$_3$	(8)	82	90-94/70mm
"	OBz(6)	OBz(9)		86	150-155/2mm
TsNHCH$_3$ (3)	Ph⌒OH	Ph⌒NTsCH$_3$	(10)	33	94-95
"	OH OH	NTsCH$_3$ NTsCH$_3$	(11)	53	oil
"	OBz(6)	OBz(12)		48	100-101
TfNHPh (4)	Ph⌒OH	Ph⌒NTfPh	(13)	41	78-79
"	OH	NTfPh	(14)	26	59-60
"	CH$_3$OH	CH$_3$NTfPh	(15)	86	oil
TsNHPh (5)	Ph⌒OH	Ph⌒NTsPh	(16)	68	139.5-140
"	OH	NTsPh	(17)	66	89-90
"	CH$_3$OH	CH$_3$NTsPh	(18)	65	93.5-94

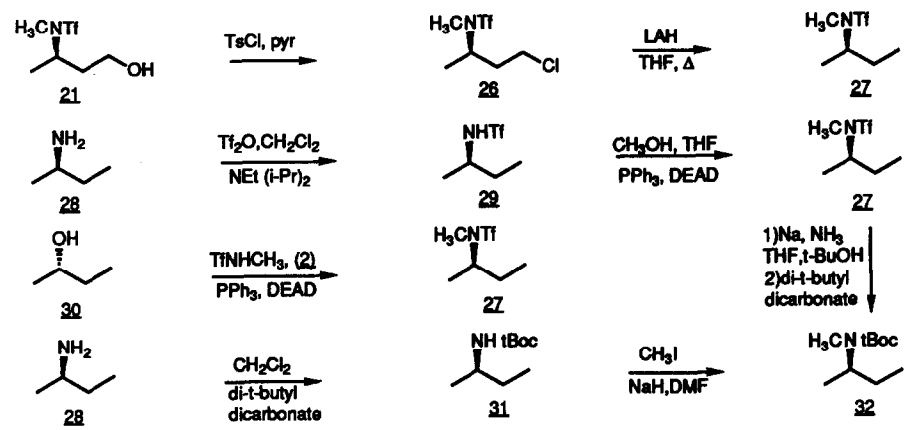
We used the Tf activating group in the preparation of the enantiomers of 1 as illustrated in Scheme 1 for the (R,R)-enantiomer 24.[16] Preliminary studies were performed using the racemic alcohol 6 (Table 1) and both Ts and Tf activating groups. When the sequence in Scheme 1 utilized Ts activated amines, two problems were encountered. First, the introduction of the Ts activated methylamine proceeded in low yield (12, Table 1). Second, the coupling in the third step of Scheme 1 using 1,7-bis-(p-toluenesulfonamido)heptane (instead of 33) and the alcohol derived from 12 (i.e., $CH_3CH(NTsCH_3)CH_2CH_2OH$) gave a mixture of mono and bis adducts. The reaction could not be forced to completion by the addition of more reagents. In contrast to the preparation of 12, introduction of Tf activated methylamine provided 9 (Table 1) in 86% yield. In addition, the coupling using 1,7-bis-(trifluoromethanesulfonamido)heptane (33) and the alcohol derived from 9 (i.e., racemic 21) gave only bis adduct in 90% yield. The (S,S)-enantiomer 25[17] was prepared by the same sequence as outlined in Scheme 1 starting with 34,[18] the (R)-enantiomer of 19.[19]

Scheme 1. Preparation of compound 24, the (R,R)-enantiomer of compound 1.



To demonstrate that the Mitsunobu reaction proceeded with inversion of configuration and that the reductive removal of the Tf group did not result in loss of chirality, we performed the transformations outlined in Scheme 2. Compound 21 was converted in two steps to (R)-(-)-2-(N-methyltrifluoromethanesulfonamido)butane (27), and the optical rotation of material prepared by this method was compared to 27 prepared in two steps from (R)-(-)-2-aminobutane (28). Also compared in this manner was 27 prepared from 2 and (S)-(+)-2-butanol (30) by the Mitsunobu reaction. Samples prepared by these methods gave $[\alpha]_D^{20}$° -13.1 (c=1.09 $CHCl_3$), -15.0° (c=1.00, $CHCl_3$) and -14.5° (c=1.07, $CHCl_3$), respectively. Compound 27 was deprotected reductively (Na, NH_3, THF, t-BuOH) and converted to the t-Boc derivative for ease of isolation to yield 32. The optical rotation of this compound was compared to 32 prepared in two steps from (R)-(-)-2-aminobutane (28). These two samples gave $[\alpha]_D^{20}$° -16.0° (c=1.04, $CHCl_3$) and -15.1° (c=1.04, $CHCl_3$), respectively.

Scheme 2. Proof of stereochemistry



In a typical procedure (S)-(+)-2-butanol (30) (0.74 g, 0.01 mol), triphenylphosphine (2.62 g, 0.01 mol) and N-methyltrifluoromethanesulfonamide (2) (1.63 g, 0.01 mol) were combined in dry THF (10 ml) under nitrogen. A solution of diethyl azodicarboxylate (1.74 g, 0.01 mol) in THF (1 ml) was added dropwise and the reaction mixture was stirred for 5-10 min. The solvent was removed at atmospheric pressure through a column of glass helices and the residue was distilled at reduced pressure to obtain (R)-(-)-2-(N-methyltrifluoromethanesulfonamido)butane (27) (1.84 g, 84%); bp 67-69°C (12 mm); $[\alpha]_D^{20}$° -14.5° (c=1.04, $CHCl_3$).

In a typical deprotection procedure, 27 (1.32 g, 0.006 mol) was combined with THF (30 ml), t-butanol (30 ml) and freshly distilled NH_3 (60 ml) at -70°C and sodium metal was added until a blue color persisted for 30 min. The reaction was warmed to 60°C under a condenser for 2 h to remove the NH_3. The residue was diluted with water (30 ml), di-t-butyldicarbonate (1.74 g, 0.008 mol) was added and the mixture was stirred for 1h. The mixture was then diluted with ether (100 ml) and the organic layer was dried and evaporated. Distillation at reduced pressure gave 32 (0.82gm, 72%) as a liquid, bp 65-70°C (0.25 mm); $[\alpha]_D^{20}$ -16.0 (c=1.04, $CHCl_3$).

In summary, we report a chiral synthesis of secondary amines from alcohols and N-alkyltrifluoromethanesulfonamides by the Mitsunobu reaction. This methodology was successfully utilized in the synthesis of the (R,R)- and (S,S)-enantiomers 24 and 25 of the antitumor polyamine (1) and represents a significant improvement over standard chiral polyamine syntheses[5,6]. Use of N-alkyl-p-toluenesulfonamides, as recently reported by Weinreb, et al[7], was unsatisfactory for the synthesis of 24 and 25. In addition, we describe a method (Na/NH_3/t-BuOH/THF) for removal of the trifluoromethanesulfonamido group and the synthesis of N-phenyl-N-alkylamines from alcohols was investigated utilizing both TfNHPh (4) and TsNHPh (5).

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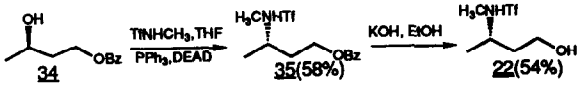
16. 24: mp 241-2°C. NMR (300 MHz, D_2O) δ 3.36 (m, 2H); 3.15 (m, 4H); 3.06 (m, 4H); 2.7 (s, 6H); 2.18 (m, 2H); 1.96 (m, 2H); 1.68 (m, 4H); 1.38 (m, 6H); 1.34 (d, 6H, J=6.5 Hz). MS (CI) m/z=301 (M+H). $[\alpha]_D^{20}$ +11.1° (c=1.0, H_2O).
17. 25: mp 241-3°C. NMR (300 MHz, D_2O) δ 3.36 (m, 2H); 3.15 (m, 4H); 3.06 (m, 4H); 2.7 (s, 6H); 2.18 (m, 2H); 1.96 (m, 2H); 1.68 (m, 4H); 1.38 (m, 6H); 1.34 (d, 6H, J=6.5 Hz). MS (CI) m/z=301 (M+H). $[\alpha]_D^{20}$ -10.3° (c=0.62, H_2O).
18. The synthesis of 22 from 34 is outlined below:



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