

Acid-labile Methylprenyl Protection for Sulfonamides

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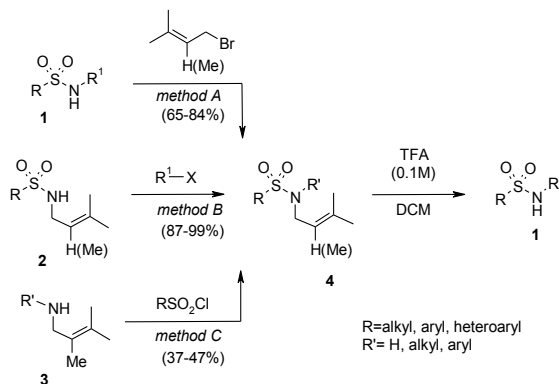
Introduction

Sulfonamide group may often require protection during the synthesis of complex compounds due to relative acidity and nucleophilicity in deprotonated form.

The installation of methylprenyl group can be realized through *N*-alkylation of sulfonamides **1** with (methyl)prenyl bromide (*method A*), *N*-alkylation or arylation of *N*-(methyl)prenyl sulfonamides **2** (*method B*) or sulfonylation of methylprenyl anilines **3** (*method C*).

Summary

Methylprenyl group is an acid-labile sulfonamide protecting group. Cleavage proceeds smoothly in the presence of TFA for aromatic and aliphatic sulfonamides. Desired products are obtained in high yields. In most cases additional purification was not required. Methylprenyl group is stable in presence of base, DDQ, NIS, LAH and to hydrogenation conditions.



Results for Deprotection

Compound	R'	Methylprenyl		Prenyl	
		Time	Yield of 1	Time	Yield of 1
	H	1 h	quant	1 h	Mix of products
	allyl	45 min	89%	1 h	78% ^b
	propargyl	12 h 1 h ^a	quant	2 h	Mix of products
	Bn	1.5 h ^a	quant	1 h	Mix of products
	Ph	20 min	quant	----	----
	4-MeOPh	1 h	quant	----	----
	tBu	12 h	Mix of products	10 h	Mix of products
	4-BnOPh	----	----	----	----
	Ph	20 min	quant	1 h	89% ^b
	Ph	12 h ^a	92% ^b	----	----
	Bn	12 h	quant	12 h	Mix of products
	Ph	1 h	91% ^b	----	----

^a concentration of TFA 0.25M, ^b isolated yield after purification/ crystallization

Stability of Methylprenyl and Prenyl group

Compound	Reaction condition	Methylprenyl (yield)	Prenyl (yield)
	DIBAL, (dppp)NiCl ₂ , toluene, rt	Selective allylgroup cleavage (89%)	Selective allylgroup cleavage (84%)
	NIS, DCM, rt	Stable	n.d.
	DDQ, DCM, H ₂ O, 24h, reflux	Stable	Stable
	BCl ₃ (1.1 eq), DCM, rt	Methylprenyl and tBu cleavage (99%)	Selective tBu cleavage (76%)
	Zn, AcOH, EtOH, 24h, rt	Stable	n.d.
	Pd/C, H ₂ (6atm), EtOAc	Reacts	Reacts
	Pd/C, H ₂ (1atm), EtOAc	Selective O-debenzylation (84%)	Reacts
	Pd(OH) ₂ , H ₂ (1atm), EtOH	Reacts	Reacts

Synthetic application

