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A Facile Preparation of Benzyltrimethylstannanes and Their Utility in the Synthesis of 1-Benzyl-1,2-dihydroisoquinolines

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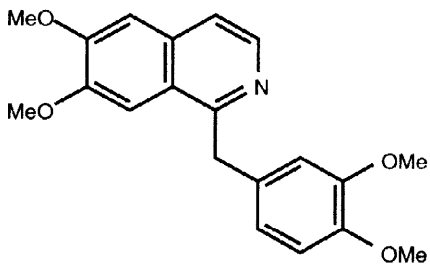
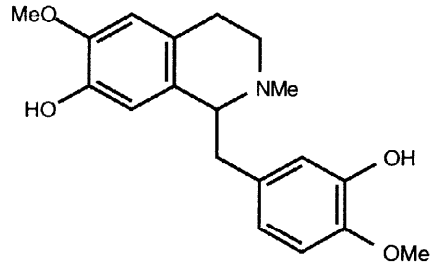
Abstract: A Barbier approach employing benzyl halides and trimethyltin chloride in the presence of magnesium metal provides a facile preparation of benzyltrimethylstannanes which react with isoquinoline in the presence of methyl chloroformate to give 1-benzyl-1,2-dihydroisoquinolines.

The 1-benzylisoquinoline nucleus is a structural feature found in a wide variety of alkaloids[1] from the fully aromatic systems such as papaverine (**1**), a common opium alkaloid (0.5 to 1% of the dry weight in opium poppies) which is clinically used as a vasodilator,[2] to the 1,2,3,4-tetrahydro systems such as reticuline (**2**), a key intermediate along the morphine biosynthetic pathway.[3]



(1)



(2)

There are a number of synthetic methodologies that have been developed for the preparation of the isoquinoline nucleus, some of which have been adapted to produce 1-benzylisoquinolines. Among the most common approaches are the Bischler-Napieralski,[4] Pictet-Spengler,[5] Pomeranz-Fritch, [6] and more recently Miller-Frincke[7] reactions. In our approach to the 1-benzylisoquinoline skeleton, we chose to explore a nucleophilic alkylation method starting with a fully aromatic isoquinoline nucleus. Using the precedence of Yamaguchi[8] and Comins,[9] we proposed to prepare 1-benzyl-N-carbomethoxy-1,2-dihydroisoquinolines by addition of organotin reagents to N-acyliminium ions derived from isoquinoline. There should be no regiochemical concern since nucleophiles favor attack at C-1 on isoquinolines or isoquinolinium salts. Furthermore, the 1-benzyl-1,2-dihydroisoquinoline products are versatile intermediates that can lead either to fully aromatic systems by hydrolysis and aromatization or to 1,2,3,4-tetrahydro systems by reduction. In addition, the presence of the N-carbomethoxy group allows either hydrolysis to a secondary amine or reduction ($LiAlH_4$) to a N-methyl group, a common structural feature in many 1-benzyl-1,2,3,4-tetrahydroisoquinoline alkaloids.

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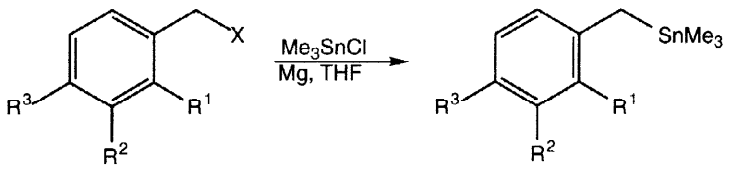
The first step in realizing our goal was to develop an efficient method for preparing the benzyltrimethylstannanes needed for these studies. Attempts using a variety of existing methods did not give acceptable yields. However, we found that a Barbier[10] approach gave excellent results. The best yields were obtained by adding the benzyl halide to an excess of trimethyltin chloride and magnesium turnings in dry THF. Using this method, the following stannanes[11] were prepared.

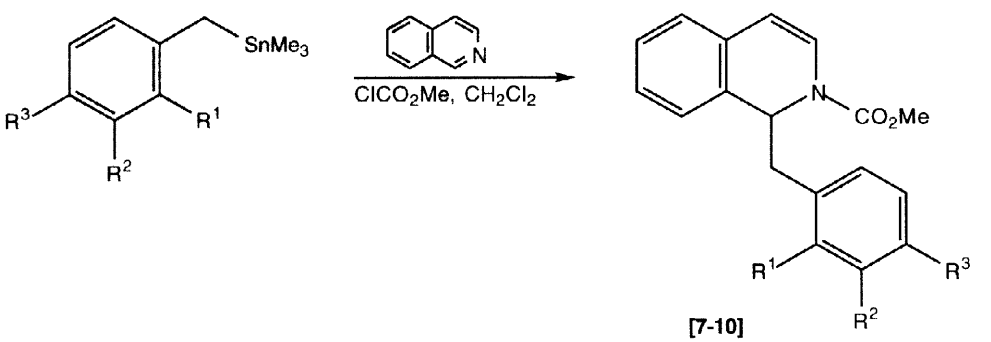


[3-6]

Compound	X	R^1	R^2	R^3	% Yield*
3	Cl	H	H	H	85
4	Br	H	OMe	OMe	80
5	Br	H	$-OCH_2O-$		80
6	Br	Me	H	H	84

*Distilled yields

With the benzylstannanes readily available, we next turned to their addition to isoquinoline. Thus we reacted the four benzylstannanes obtained above with isoquinoline and methyl chloroformate in dichloromethane. This nucleophilic alkylation proceeded smoothly to give moderate to good yields of the desired 1-benzyl-N-carbomethoxy-1,2-dihydroisoquinolines,[11] as can be seen below.



[7-10]

Compound	R^1	R^2	R^3	% Yield*
7	H	H	H	56
8	H	OMe	OMe	52
9	H	$-OCH_2O-$		71
10	Me	H	H	53

*Purified yields

Initially, the ^{1}H–NMR of the dihydroisoquinoline products was confusing because two sets of peaks appeared for almost all of the absorptions. Variable temperature studies showed that this was due to hindered

rotation around the amide bond. As the temperature of the probe was increased (25° → 80°C), the dual spectrum coalesced into one.

GENERAL EXPERIMENTAL PROCEDURES

Benzyltrimethylstannanes: 3,4-Dimethoxybenzyltrimethylstannane (**4**) is described as a typical example. Trimethyltin chloride (2.00 g, 10.0 mmol) was dissolved in dry THF (5 mL) and added to a flask containing magnesium turnings (600 mg, 24 mmol). The mixture was heated to 60°C [for benzyl chloride, a couple of drops of 1,2-dibromoethane were used to initiate the reaction] and 3,4-dimethoxybenzyl bromide (1.50 g, 6.49 mmol) dissolved in dry THF (10 mL) was added dropwise *via* an addition funnel. The mixture was refluxed for an additional 3 hours. The reaction was cooled in an ice-bath, quenched with water, and extracted with diethyl ether. The combined organic fractions were washed with 5% HCl, water and brine and dried over anhydrous Na_2SO_4. After removal of the solvent, the remaining material was subjected to Kugelrohr distillation (80°C, 0.1 torr) to give 1.63 g (80% yield) of (**4**)[11] as a colorless product.

1-Benzyl -N-carbomethoxy-1,2-dihydroisoquinolines: 1-(3,4-Methylenedioxybenzyl)-N-carbomethoxy-1,2-dihydroisoquinoline (**9**) is described as a typical example. Isoquinoline (200 mg, 1.55 mmol), 3,4-methylenedioxybenzyltrimethylstannane (**5**, 400 mg, 1.34 mmol) and dichloromethane (5 mL) were combined in a 25 mL round-bottom flask. The resulting solution was cooled in an ice-bath and then methyl chloroformate (200 μL, 245 mg, 2.59 mmol) was added *via* syringe. [Usually after about 5 minutes a pale-yellow precipitate formed.] The solution was allowed to come to room temperature and stirred overnight [at which point it was homogeneous]. Water was added and the mixture was stirred for 45 minutes followed by extraction with ethyl acetate. The combined organic fractions were washed with 5% HCl, water, saturated $NaHCO_3$ solution, and brine and dried over anhydrous Na_2SO_4. Removal of the solvent gave a colorless oil which was chromatographed on silica gel to give pure (**9**)[11] as a white solid (307 mg, 71% yield) with m.p. 119-120°.

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11. Satisfactory spectroscopic (NMR and IR) and analytical (elemental and/or mass spectral) data were obtained for these compounds.