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The Synthesis of $GABA_A$ Active Ligands by the Stille Process

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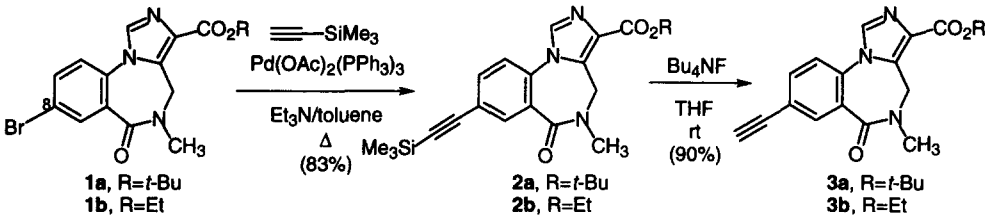
Abstract: *A variety of $GABA_A$ active analogs **3b-3h** with different substituents at C(8) of the imidazobenzodiazepine nucleus was synthesized via the Stille coupling reaction. In addition, stannane **4** was prepared which provides facile entry into other members of the series.* © 1997 Elsevier Science Ltd.

The $GABA_A$/benzodiazepine receptor ($GABA_A$/BzR) is a heterooligomeric family of ligand gated ion channels which constitutes the major inhibitory neurotransmitter system in the mammalian central nervous system.[1] This membrane-bound protein complex plays a central role in the molecular mechanisms which underlie anxiety, sleep, convulsions and cognition; consequently, it represents an important target for the design of selective agents to treat specific disease states in the CNS. Presently, a total of 6α, 3β, 3γ, 1δ and 2ρ subunits, which have been isolated from various $GABA_A$ receptor isoforms from the mammalian CNS, have been cloned and sequenced.[1] Among these, α1β2γ2 represents the classical Type-I BzR, while α2β2γ2, α3β2γ2 and α5β2γ2 ion channels are termed Type-II BzR.[2,3] The closely related α4β2γ2 and α6β2γ2 channels both resemble "diazepam-insensitive" sites,[4-6] the latter of which has been studied extensively.[7-12] The extensive molecular diversity of $GABA_A$/BzRs which results from these subunits has been implicated in the multiple pharmacological properties elicited by ligands which lack subtype selectivity, such as diazepam.[1,13-16] Furthermore, the regional heterogeneity of $GABA_A$/BzR subtypes has also been suggested as a basis for the multiplicity of pharmacological properties of the benzodiazepines.[1,16]

Recently, the synthesis of a series of C(8)-substituted imidazobenzodiazepines which exhibit high affinity ($K_i \approx 0.4$-5 nM) and selectivity for recombinant α5-containing $GABA_A$ receptors by a Heck-type coupling reaction[17] was reported.[18,19] For example, as illustrated in Scheme 1, the 8-bromobenzodiazepine templates **1a-b**[7] were coupled with acetylenetrimethylsilane in the presence of bis(triphenylphosphine)-palladium(II) acetate (10 mol %) to provide trimethylsilyl analogs **2a-b** in 83% yield. Treatment of **2a-b** with Bu_4NF effected the desilylation to furnish the 8-acetylenebenzodiazepines **3a-b** in 90% yield. Substitution of an acetylene unit at C(8) of the imidazobenzodiazepine nucleus has provided the most selective ligands reported to date for the α5-containing $GABA_A$ receptors (67-fold for **2a** and 60-fold for **2b**). The α5-containing isoforms have been found principally in the hippocampus[20,21] which is involved in memory and learning (cognition).[22-24] Moreover, the action *in vivo* of these ligands resembled that of inverse agonists (convulsants/proconvulsants).

Scheme 1



In order to readily expand the SAR of these imidazobenzodiazepines at C(8), it was decided to prepare a number of analogs by utilization of the Stille coupling reaction.[25,26] This process has been employed widely to functionalize an aromatic ring with vinyl, allyl or aryl groups *via* organotin compounds and Pd catalysts.[25,26]

Scheme 2

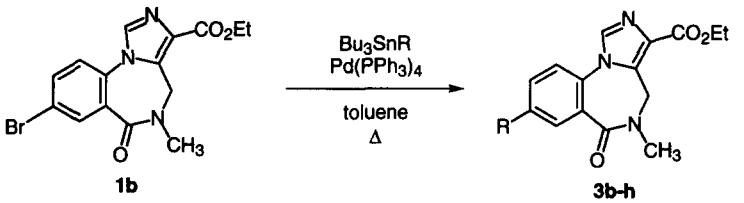
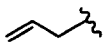


Table 1. Stille coupling reactions of **1b** with tributyltin reagents.

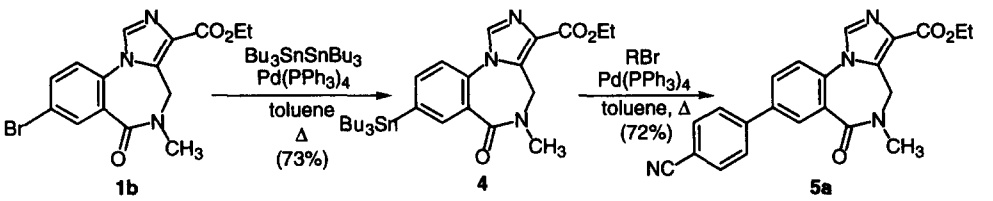
	R	time (h)	yield (%)
3b		6	50
3c		2	90
3d		4	95
3e		4	72
3f		4	83
3g		2	92
3h		3.5	94

As illustrated in Scheme 2, 8-bromobenzodiazepine **1b** was treated with a variety of tributyltin reagents in the presence of tetrakis(triphenylphosphine) palladium(0) as a catalyst. A typical reaction

procedure is illustrated here. A mixture of bromide **1b** (0.41 mmol, 1 eq.), tributyltin reagent (1.1 eq) and $Pd(PPh_3)_4$ (0.03-0.05 eq.) in dry toluene (5 mL) was heated to reflux under N_2 for a period of several hours (as shown in Table 1). The color of the solution changed from yellow to black and Pd(0) precipitated from the medium. The mixture was diluted with EtOAc (50 mL) and washed with a 15% aqueous solution of KF. The organic layer was separated and dried (K_2CO_3). After removal of the solvents, the residue was purified by flash chromatography (silica gel, EtOAc) to provide the C(8)-substituted imidazobenzodiazepines represented by **3**. A variety of vinyl, allyl and aryl tributyltin reagents underwent the Stille coupling reaction to give C(8)-substituted benzodiazepines **3b-h** in good to excellent yield (Table 1). The α5 selective ligand **3b** was also prepared in one step. Initial *in vitro* pharmacology indicated that vinyl analog **3c** exhibited very good affinity ($K_i \approx 0.4$ nM) and some selectivity (21-fold) for recombinant α5-containing $GABA_A$ receptors as compared to the acetylene analog **3b**.

In addition, as illustrated in Scheme 3, 8-stannylimidazobenzodiazepine **4** was prepared in 73% yield and characterized by heating bromide **1b** with bistributyltin in the presence of $Pd(PPh_3)_4$.[27] Stannane **4** is now available to react with a variety of common coupling partners including vinyl, allyl, aryl, and acyl halides as well as aryl and vinyl triflates to provide more analogs for the study of α5 containing $GABA_A$ receptors. For example, stannane **4** was stirred with 4-bromobenzonitrile to provide **5a**.

Scheme 3



In summary, the Stille coupling reaction has been employed for the synthesis of a number of analogs with a variety substituents at C(8) of the imidazobenzodiazepine nucleus of **1b**. These reactions, as expected, occurred in good to excellent yield. In addition, the preparation of stannane **4** will provide facile entry into a host of important analogs for biological screening at $GABA_A$/Bz receptors.

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(27) **4**: ^1H NMR (250 MHz, $CDCl_3$) δ 0.86 (t, 9H, J = 7.2 Hz), 1.02-1.58 (m, 21H), 3.22 (s, 3H), 4.41 (q, 2H, J = 6.8 Hz), 4.43 (s, br, 1H), 5.14 (s, br, 1H), 7.32 (d, 1H, J = 7.7 Hz), 7.67 (d, 1H, J = 7.7 Hz), 7.85 (s, 1H), 8.10 (s, 1H); MS (CI, CH_4) *m/e* (relative intensity) 576 (M+1, 100).

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