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A new synthetic approach to 2-substituted putrescines

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Abstract

An efficient methodology for the synthesis of 2-substituted putrescines is described. The key step of our approach utilized a coupling reaction of a stereodefined vinylstannane **2**, easily derived from 1,4-diaminobut-2-yne **1**.

1,4-Diaminobutane (putrescine) was recognized as an important natural polyamine, and together with its derivatives, spermidine and spermine, became part of a group of substances deeply involved in cell proliferation and in vivo protein synthesis.[1] In animal cells, these compounds are synthesized from ornithine in a reaction catalyzed by ornithine decarboxylase (ODC). Irreversible inhibitors of ODC, which cause a reduction in the cellular concentration of polyamines have been shown to have potential for treating diseases associated with rapid cell proliferation.[2] In this context, numerous synthetic analogues and derivatives of the natural polyamines have been prepared. In particular, 2-substituted putrescines were found to be competitive inhibitors of ODC, as well as inhibitors of the diamine oxidases of plant and mammalian origin.[3]

To our knowledge, only one general synthesis of these compounds was reported by Frydman et al. from 3-alkylpyrroles.[4] Nevertheless, this synthetic approach required eight steps and is restricted to 2-alkylputrescines. In the course of our ongoing program related to the synthesis of polyamine derivatives,[5] we have developed an efficient and straightforward methodology for the synthesis of 2-alkyl- and arylputrescines from the 1,4-diaminobut-2-yne **1**. This approach also permitted an easy access to 2-substituted dehydro-putrescines which are known to possess antifungal activities.[6] After protection of **1** as its *N*-di-*tert*-butyloxycarbonyl derivative, hydrostannation in the presence of a catalytic amount of $Pd(PPh_3)_4$ at room temperature afforded the corresponding vinylstannane **2** in a 95% yield.[7,8]

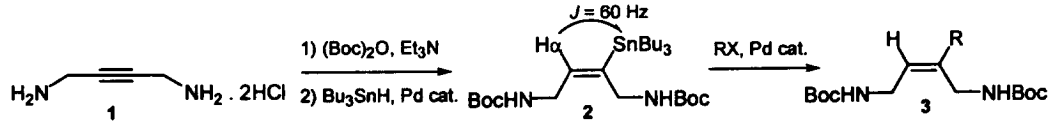

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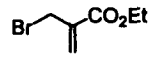
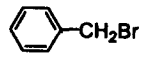
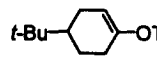
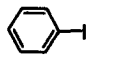
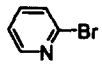
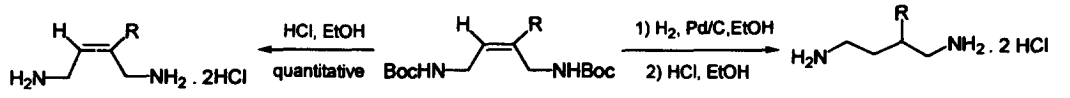
Table 1
Cross-coupling of **2** with various electrophiles

Entry	Electrophiles	Conditions[a]	Yield[b] (%)
a		$Pd(PPh_3)_4$, toluene, reflux, 20h	60
b		$Pd(PPh_3)_4$, toluene, reflux, 16h	65
c		$Pd(PPh_3)_4$, toluene, reflux, 20h	95
d		Pd_2dba_3, $AsPh_3$, LiCl, NMP, 60°C, 72h	37
e		Pd_2dba_3, $AsPh_3$, CuI, NMP, 50°C, 17h	40
f		Pd_2dba_3, $AsPh_3$, CuI, NMP, 80°C, 48h	40

[a] Reactions were carried out with 0.5-1 mmol of each reagent in 2 ml of solvent and 1-2 mol % catalyst. [b] yields after chromatographic purification. All compounds exhibit consistent ^1H and ^{13}C NMR, and mass spectra.

The reaction is highly stereoselective (*syn* addition deduced from the small ^3J coupling constant between Sn and H_α (60 Hz)). Cross-coupling reaction of **2** with different electrophiles (Table 1)[9,10] in the presence of palladium catalyst provided the corresponding 2-substituted-1,4-di-*tert*-butyloxycarbonylaminobut-2-enes **3**. Moderate to good yields of geometrically pure alkenes were obtained. Aryl triflate and halide reacted with stannane **2** in fair yields using triphenylarsine instead of triphenylphosphine (entries d–f).

2-Alkyl- and arylputrescines **4** resulted from the catalytic hydrogenation of **3** in ethanol over 10% Pd/C at 70 bar, followed by deprotection of the *N*-Boc groups. Alternatively, stereodefined 2-substituted dehydro-putrescines **5** were quantitatively obtained by aqueous hydrochloric acid hydrolysis. Extension of the use of the stannane **2** in synthesis, and biological studies of **4** and **5** will be reported in due course.



5 **3**

4a, R = *n*-C_3H_7 (81%)
4b, R = $CH_2CH(CH_3)CO_2Et$ (61%)
4c, R = CH_2Ph (90%)
4d, R = 4-*tert*-butylcyclohexyl (77%)
4e, R = Ph (91%)
4f, R = 3-pyridinyl (70%)

Acknowledgements

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