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Intramolecular Aminopalladation and Cross Coupling of Acetylenic Amines

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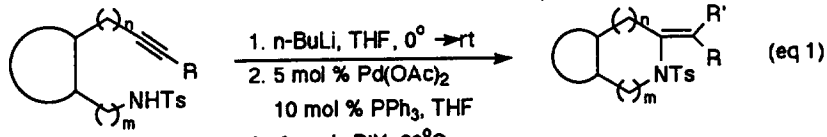
Abstract: Stereodefined 2-alkylidene-pyrrolidines and -piperidine were synthesized by treatment of an acetylenic amines with n-BuLi followed by addition of catalytic amount of $Pd(OAc)_2$ and PPh_3 in THF and 3 equiv of an organic halide.

The formation of stereodefined 2-alkylidene-pyrrolidine or -piperidine derivatives is still a synthetic challenge. Intra- and inter-molecular reactions of acetylenic amines with palladium catalyst have developed in several efficient processes leading to the formation of a variety of heterocycles.[1-5] However, the synthesis of stereodefined 2-alkylidenepyrrolidine or -piperidine from acetylenic amines, as to our knowledge, has not been reported before. Recently, we have reported a procedure for preparing stereodefined 2-alkylidenetetrahydrofurans and pyrans from alkyl or aryl acetylenic alcohols.[6] We now report that stereodefined 2-alkylidene pyrrolidine and piperidine derivatives can also be efficiently synthesized from acetylenic amines by the similar procedure (eq 1).

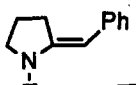
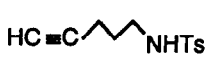
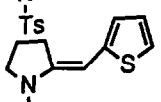
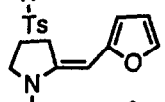
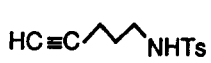
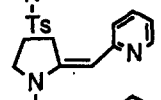
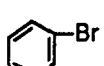
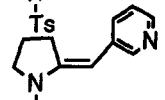
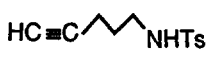
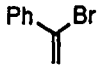
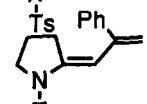
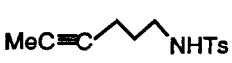
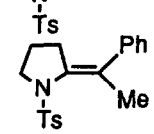
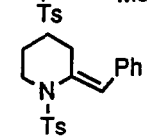
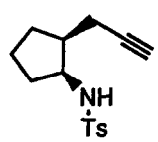
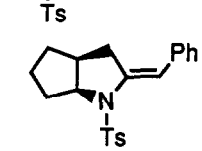
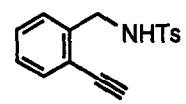
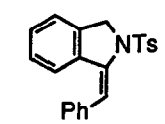


(eq 1)

n = 1, 2. m = 0,1.
R = H, Me. R' = phenyl, heteroaryl, alkenyl.

The experimental results are summarized in Table I. It demonstrated that a wide range of pyrrolidine or piperidine derivatives with stereodefined exocyclic double bond can be formed through this cyclization and coupling reaction. Several features are noteworthy. The reaction by using primary amine, e.g. pent-4-ynylamine, with or without treatment of n-BuLi, failed to give any detectable amount of the desired product in GLC as well as ^1H NMR spectrum analysis. Probably the stabilized anion of sulfonamide has greater nucleophilicity and lower basicity than the corresponding non-stabilized amide anion.[7] When iodomethane was used as the coupling reagent, under the reaction conditions, only N-methyl-N-pent-4-

Table I. Intramolecular Aminopalladation and Cross-Coupling of Acetylenic Amines via Palladium Catalyst

Entry	Substrate[8-10]	RX	Product[a]	Yield (%)
1		PhI		57
2				86
3				86
4				63
5				84
6				72
7		PhI		62
8		PhI		58
9		PhI		85
10		PhI		63

[a] All compounds are characterized by mass spectrometry, IR, ^{1}H and ^{13}C NMR spectroscopy.

ynylamine was isolated in 73% yield, no cyclized and coupling product was detected. Probably the N-alkylation step is much faster than the reversible cyclization and coupling processes. On the contrary, the coupling with phenyl iodide, heteroaryl iodide, or alkenyl halide without facing any difficulities. Both iodides and bromides are good electrophiles for the coupling process. No migration of the exocyclic double bonds was found in the reactions indicating that their stabilities were quite high in these products. Both five- or six-membered rings with high regio- and stereoselectivities can be formed under the reaction conditions. However, the forming of tetrasubstituted exocyclic double bond or six-membered ring was slower than the other cases (entries 7 and 8). Attempts to cyclize N-but-3-ynyl-4-methyl-benzenesulfonamide to give four- or five-membered ring product failed under various conditions.

The following procedure for the synthesis of (*E*)-(2-thiophene-2-ylmethylene-pyrrolidine-1-yl)-p-tolylsulfone is representative. A solution of n-BuLi (1.4 mL of 1.6 M in hexane, 2.2 mmol) was added dropwise to a solution of N-pent-4-ynyl-(4-methylbenzene)sulfonamide[8] (0.48 g, 2 mmol) in 4 mL of THF at 0°C under a nitrogen atmosphere. To the reaction mixture was added a solution of $Pd(OAc)_2$ (23 mg, 0.1 mmol) and PPh_3 (53 mg, 0.2 mmol) in 2 mL of THF and then 2-iodothiophene (1.26 g, 6 mmol). The reaction mixture was then stirred at 60°C for 8 h and then quenched with water (10 mL). The organic layer was separated, and the aqueous layer was extracted with methylene chloride. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to give a pale yellow solid, which was further purified by column chromatography (silica gel, ether/ hexane = 1:3) to give the desired product (0.55 g, 86%) as a pale yellow solid (mp 124.5-125.5°C). ^1H NMR ($CDCl_3$, TMS) δ 1.82 (m, 2 H), 2.40 (s, 3 H), 2.59 (dt, J = 7.4, 2.0 Hz, 2 H), 3.67 (t, J = 6.9 Hz, 2 H), 6.88 (d, J = 3.5 Hz, 1 H), 6.99 (dd, J = 5.1, 3.5 Hz, 1 H), 7.07 (t, J = 2.0 Hz, 1 H), 7.15 (d, J = 5.1 Hz, 1 H), 7.27 (d, J = 6.6 Hz, 2 H), 7.73 (d, J = 6.6 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, TMS) δ 21.42, 21.88, 30.42, 50.80, 103.66, 123.34, 125.21, 126.98, 127.20, 129.50, 134.35, 138.73, 140.76, 143.94 ppm. MS m/z 319 (M^+), 262, 202, 164, 84. IR ($CHCl_3$) ν 3030 (w), 2880 (w), 1640 (m), 1590 (w), 1340 (s), 1200 (w), 1155 (s), 1090 (s), 1000 (m), 950 (m), 750 (m), 690 (m), 590 (m) cm^{-1}. The stereoisomeric purity was ≥98% as determined by ^1H and ^{13}C NMR spectra. The relative stereochemistry of the vinyl proton and the allylic proton was determined by ^1H-2D NOESY NMR spectrometry (entry 2).

The results reported probably involves sequential (1) proton abstraction from the amine, (2) complexation of the oxidative Pd(II) adduct with

the triple bond followed by trans-aminopalladation, and finally (3) reductive elimination to produce the product and regenerate the palladium catalyst. Application of this procedure for the synthesis of other heterocycles containing two or three heteroatoms is underway.

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8. N-Pent-4-ynyl-(4-methylbenzene)sulfonamide, N-hex-4-ynyl-(4-methylbenzene)sulfonamide, and N-hex-5-ynyl-(4-methylbenzene)sulfonamide were synthesized in 62-73% total yields from 3-butyn-1-ol, 3-pentyn-1-ol, and 4-pentyn-1-ol, respectively, in four steps: tosylation (n-BuLi, THF; TsCl, THF), cyanization (2 equiv NaCN, MeOH, reflux), reduction (LAH, ether), and tosylation (n-BuLi, THF; TsCl, THF).
9. cis-N-(2-Prop-2-ynyl-cyclopentyl)-(4-methylbenzene)sulfonamide was synthesized in 48% yield from cyclopentene oxide via ring opening (allenylmagnesium bromide)[11], amine formation (PPh_3, phthalimide, diethyl azodicarboxylate; hydrazine),[12] and tosylation (n-BuLi, THF; TsCl).
10. N-(2-Ethynyl-benzyl)-(4-methylbenzene)sulfonamide was synthesized in 50% yield from 2-bromotoluene via cross coupling (cat. $Pd(PPh_3)_4$, trimethylsilylethynylzinc chloride),[13] benzylic bromination (cat. $(PhCO_2)_2$, NBS, CCl_4), amine formation and desilylation ($NaNH_2$, NH_3), and tosylation (n-BuLi, THF; TsCl, THF).
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