

ortho-Vinylation reaction of anilines

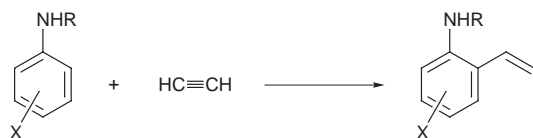
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N-Alkylanilines and anilines are vinylated at the ortho-position with ethyne in the presence of SnCl₄-Bu₃N.

Vinylanilines are versatile intermediates for the synthesis of heterocyclic compounds and functionalized polymers, and the elimination reaction of (aminophenyl)ethanol derivatives is the most common method used to prepare these compounds.¹ The Wittig reaction has also been used for the formation of aryl olefins.² The vinyl group can be introduced to haloanilines employing either the Heck reaction or the Stille coupling reaction.³ Cleavage of heterocyclic compounds has also been examined.⁴ In some cases, such sequences of reactions were conducted *via* vinylated nitroarenes.⁵ All these methods, however, required stepwise transformations, and direct introduction of the vinyl group to the aniline nucleus was desired. In this context, the vinylation of cyclopalladated acetanilide reported by Horino is interesting, although the use of a stoichiometric amount of the palladium compound is inconvenient from a synthetic point of view.⁶ Previously, we reported the direct *ortho*-vinylation of phenols with ethyne,⁷ and the methodology is extended here to the direct *ortho*-vinylation of anilines (Scheme 1).



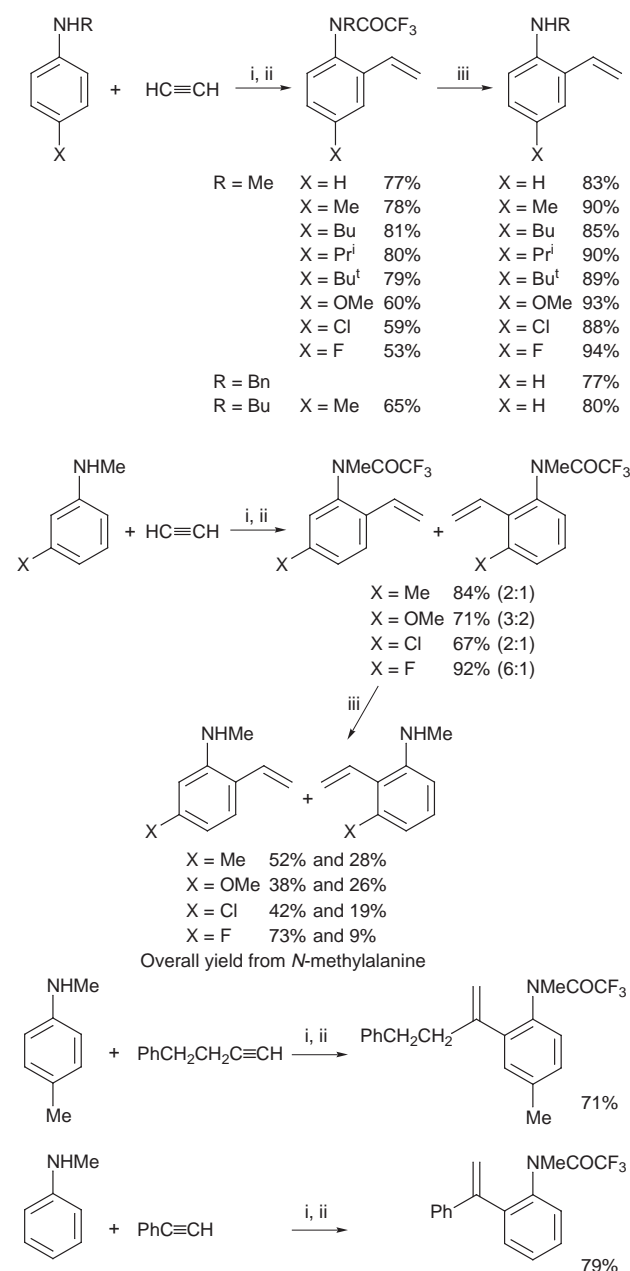
Scheme 1

Ethyne was bubbled into a chlorobenzene solution of *N*-methylaniline and SnCl₄-Bu₃N (4 equiv.) at -50 °C for 30 min. Then, the mixture was heated at 80 °C for 40 min, during which time ethyne was continuously introduced. The reaction was quenched by treating with 2 M KOH and THF at reflux for 1 h. After aqueous workup, the crude products were trifluoroacetylated with TFAA and Et₃N giving *N*-methyl-2'-vinyl trifluoroacetanilide in 77% yield. In contrast to the vinylation of phenol, the aniline reaction required the continuous introduction of ethyne during heating to obtain satisfactory results.

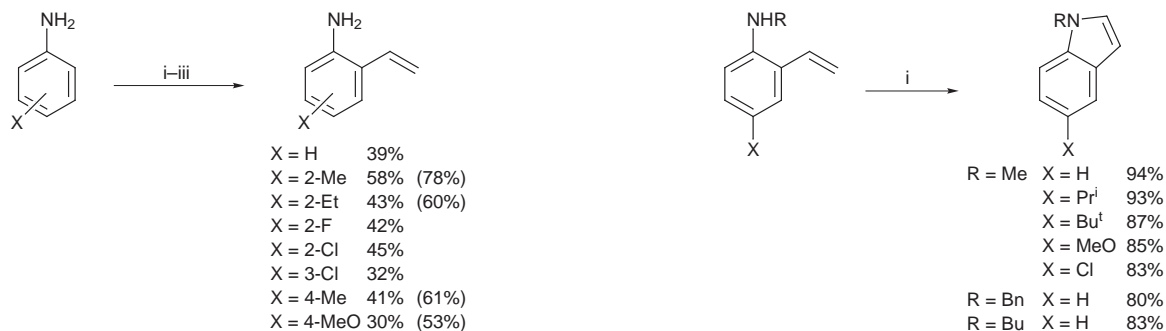
Several *para*- and *meta*-substituted *N*-methylanilines were treated with ethyne under the above conditions, and the results are summarized in Scheme 2. The vinylation was applicable to various substituted *N*-alkylanilines including halogen and methoxy derivatives. *N*-Benzyl- and *N*-butyl-aniline could also be vinylated. In the case of *meta*-substituted derivatives, the reaction took place at the less hindered site predominantly. It may be interesting to note that 3-fluoroaniline showed higher selectivity than the chloro derivative, and electronic effect also appeared to affect the selectivity. *ortho*-Substituted anilines such as 2-methyl-*N*-methylaniline did not give the expected product. This may be due to steric reasons, since *ortho*-substituted anilines lacking the nitrogen substituent gave the vinylated products (*vide infra*). Absence of the divinylated product in the reaction of *N*-methylanilines could be ascribed to the same reason.⁸ The trifluoroacetyl group could readily be removed by treatment with KOH and MeOH at reflux for 10

min. The present methodology was also used to alkenylate *N*-methylanilines with aromatic and aliphatic alk-1-yne.

The vinylation of anilines lacking the nitrogen substituent required modification of the workup procedures. *para*-Methylaniline was treated with ethyne at 80 °C for 2 h, and worked up in 2 M KOH and THF in the presence of excess ethylenediamine at reflux for 5–8 h to give a mixture of 2-vinylaniline,



Scheme 2 Reagents and conditions: i, SnCl₄-Bu₃N; ii, TFAA, Et₃N; iii, KOH, MeOH

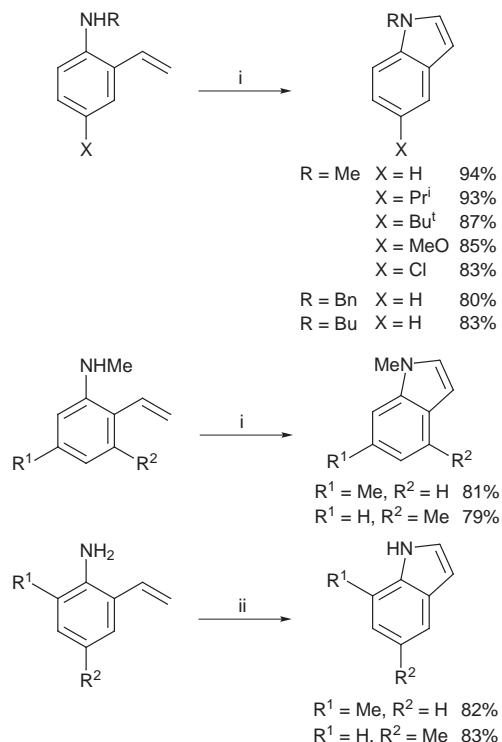


Scheme 3 Reagents and conditions: i, $\text{SnCl}_4\text{-Bu}_3\text{N}$, $\text{HC}\equiv\text{CH}$; ii, TFAA, Et_3N ; iii, KOH, MeOH, H_2O . Yields shown in parentheses are based on consumed aniline.

2,6-divinylaniline and the starting material in yields of 46, 5 and 23%, respectively. The chelating reagent was required in the workup for the effective protonation of vinylstannane, which is an intermediate of the present vinylation reaction.^{7,8} The protonation of the organotin compound appeared to be slower for vinylanilines than for *N*-methylvinylanilines and vinylphenols. The considerable amount of starting material recovered is not due to nitrogen protonation, since aniline hydrochloride could be converted to the vinylaniline. *N*-Vinylation was also excluded since reactions of alk-1-yne with *para*-methylaniline gave no trace of the corresponding methyl ketones. When 4-methylaniline was treated with the $\text{SnCl}_4\text{-Bu}_3\text{N}$ in $\text{C}_6\text{D}_5\text{Cl}$, at least two species were detected by ^1H NMR spectroscopy. Probably only a part of the stannylated aniline could participate in the vinylation. The secondary trifluoroacetamide moiety of these products hydrolyzed more slowly than the *N*-methyl derivatives, and harsh conditions were required: heating with KOH in MeOH- H_2O (96:4) for 35–48 h. Based on these experiments a method to convert anilines to *ortho*-vinylanilines was established which involved vinylation, trifluoroacetylation and deprotection (Scheme 3). The synthesis gave the vinylated products in moderate overall yields.

Vinylaniline derivatives are one of the most attractive precursors for the synthesis of indoles. While sulfonylated anilines are known to cyclize effectively,⁹ the reaction of unprotected aniline is rare. Although Hegedus reported the palladium-catalyzed reaction of *ortho*-vinylaniline,⁹ their applicability remained unexplored. When 2-vinyl-*N*-methylanilines prepared in the present study were treated with $\text{PdCl}_2(\text{MeCN})_2$ at THF reflux for 18 h in the presence of quinone and LiCl, *N*-methylindoles were obtained in high yields (Scheme 4). A shorter reaction time of 10 h was employed for 2-vinylanilines to avoid decomposition. Thus, the applicability of the Hegedus method turned out to be broad.

Typical procedures are as follows. Ethyne was bubbled into a solution of Bu_3N (24.0 mmol, 5.76 ml), SnCl_4 (24.0 mmol, 2.76 ml) and *N*-methylaniline (6.0 mmol, 642.6 mg) in chlorobenzene (60 ml) at -50°C for 1 h. The reaction mixture was heated at 80°C for 1.5 h, during which bubbling was continued. 2 M KOH (240 ml) and THF (40 ml) were added, and the mixture was heated at reflux for another 1 h. On cooling the organic materials were extracted with Et_2O , washed with brine, dried over MgSO_4 and filtered. After removal of Et_2O under reduced pressure, Et_3N (8.4 ml) and TFAA (8.5 ml) were added to the resultant chlorobenzene solution, and the mixture was stirred at -10°C for 12 h. An aqueous workup followed by flash chromatography (hexane- EtOAc , 30:1) over silica gel gave *N*-methyl-2'-vinyl trifluoroacetanilide (72%, 990 mg).



Scheme 4 Reagents and conditions: i, $\text{PdCl}_2(\text{MeCN})_2$, THF, reflux, 18 h; ii, $\text{PdCl}_2(\text{MeCN})_2$, THF, reflux, 10 h

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Notes and References

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