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Chemoselective vinylation of aminophenols with acetylene catalyzed by sodium aminophenolates in aqueous DMSO

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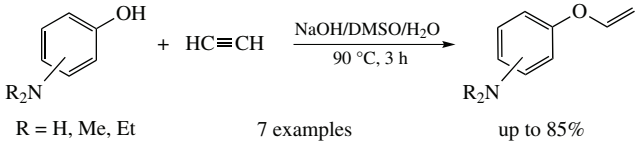
An efficient atom-economic chemoselective synthesis of vinyloxyanilines from aminophenols and acetylene catalyzed by sodium aminophenolates in aqueous DMSO (90 °C, 3 h) has been developed.



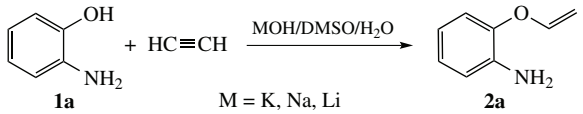
Keywords: acetylene, aminophenols, superbases, nucleophilic addition, vinylation, vinyloxyanilines.

Aminophenols belong to pharmacologically important compounds.[1] Derivatives of *p*-aminophenol find application as nonsteroidal anti-inflammatory drugs (Paracetamol, Phenacetin).[2] *S*ome derivatives of sterically hindered *o*-aminophenols have antiviral activity against the herpetic injuries of various types (Butaminophen).[3] They are also used as stabilizers for chlorine-containing thermoplastics, mild reducing agents in photography, to produce dyes, color film, for hair dyeing.[4] At the same time, less attention has been paid to their vinyl ethers, although derivatization with the enol moiety is an effective targeted modification of useful molecules including drug precursors. The vinyloxy group itself is of fundamental importance in organic chemistry. Enol ethers are flexible intermediates in a wide variety of chemical transformations [*e.g.*, cycloaddition, addition of diverse X–H-acids (X = O, N, S, P, *etc.*), rearrangement and metathesis processes],[5] as well as in the synthesis of polymers.[6] In particular, vinyl ethers of aminophenols are promising monomers for the preparation of heat-resistant ion exchange resins and semiconductors.[7]

Several synthetic approaches to aryl vinyl ethers have been documented.[8–13] However, the syntheses of vinyloxyanilines by the conventional methods are limited since both amino and hydroxy groups in aminophenols are prone to vinylation *via* nucleophilic addition to acetylenes. Besides, all the known examples were demonstrated on a milligram scale.

Meanwhile, the base-catalyzed addition of cheap and available aminophenols to acetylene seems to be a straightforward larger-scale route to vinyloxyanilines. However, such a technology remains so far underdeveloped. In a few examples of reported syntheses, there appeared certain hurdles.[14] In particular, the reactions should be carried out under harsh conditions (acetylene pressure 20–50 atm, temperature 180–220 °C) with KOH as a catalyst in aqueous dioxane or without solvent. In all the cases, oligomerization of acetylene took place also with participation of NH_2-group that complicates isolation and purification of the target products.

Therefore, optimization of this methodology represents an obvious synthetic challenge. Recently, we have developed the direct nucleophilic addition of phenols to acetylene promoted by inexpensive KOH/DMSO superbase catalytic system to afford aryl vinyl ethers in a yield of up to 80%.[15] Reducing reaction temperature by more than 50 °C and decreasing the operating acetylene pressure (owing to special superbasicity catalytic effect and high solubility of acetylene in DMSO) essentially improved feasibility of the process and made it superior over the before-existing procedures. In this paper, we disclose the efficient atom-economical synthesis of vinyloxyanilines from aminophenols and acetylene catalyzed by sodium aminophenolates in aqueous DMSO. Unlike the patent disclosure,[16] here for the first time we focus on the essential experimental details and principal peculiarities of the process, which help it to be reproducible. At the outset of our study, we examined the reaction of 2-aminophenol **1a** with acetylene as a model reaction (Scheme 1).



Scheme 1

Before charging the pressure reactor, the reaction mixture was prepared by stirring phenol **1a** and MOH (M = K, Na, Li) in DMSO/H_2O (1 : 0 or 4 : 1, v/v) to give a homogeneous solution of the corresponding phenolate. The reaction was carried out under acetylene pressure (14–16 atm). Figure 1 shows typical curves of

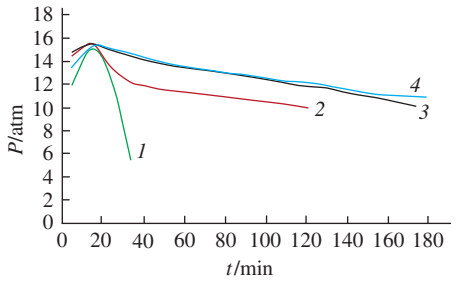


Figure 1 The absolute pressure *vs*. time for vinylation of 2-aminophenol **1a** (initial pressure of acetylene at ambient temperature 14–15 atm): (*1*) KOH (50 mol%)/DMSO, 120 °C; (*2*) KOH (50 mol%)/DMSO, 90 °C; (*3*) KOH (50 mol%)/DMSO/H_2O (4 : 1), 90 °C; (*4*) NaOH (50 mol%)/DMSO/H_2O (4 : 1), 90 °C.

Table 1 Vinylation of 2-aminophenol **1a** with acetylene: effect of various reaction parameters on the yield of vinyl ether **2a**.[a]

Entry	MOH (mol%)	DMSO/ml	H_2O/ml	*T*/°C	Time/h	Yield of **2a** (%)[b]
1	KOH·0.5H_2O (50)	50	0	120	0.25	28[c]
2	KOH·0.5H_2O (50)	50	0	105	1	30[c]
3	KOH·0.5H_2O (50)	50	0	90	2	45
4	KOH·0.5H_2O (50)	40	10	90	3	65
5	**NaOH (50)**	**40**	**10**	**90**	**3**	**77**
6	NaOH (50)	40	10	90	4	73
7	NaOH (100)	40	10	90	3	50
8	NaOH (30)	40	10	90	3	59
9	NaOH (50)	35	15	90	3	48
10	NaOH (50)	40	10	80	3	58
11	LiOH (50)	40	10	90	3	39

[a] Reagents and conditions: phenol **1a** (50 mmol, 5.45 g), initial pressure of acetylene at ambient temperature was ~14–16 atm and maximal pressure at the reaction temperature was ~14–15 atm (stirred reactor). [b] Isolated yield after distillation. [c] Much tar was formed.

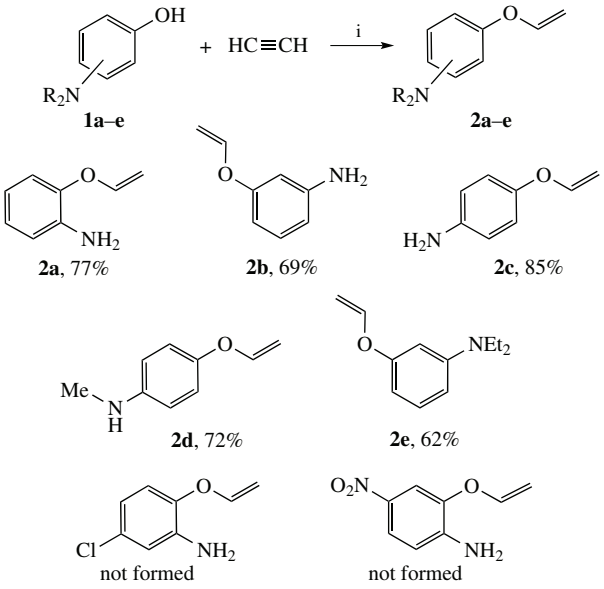
the change in acetylene pressure in the course of reaction at various temperatures. After acetylene was fed into the reactor at room temperature, the pressure dropped from 14–16 atm (initial pressure in the commercial acetylene cylinder) to 3–4 atm due to its dissolution. When the reactor was heated, the pressure rose to reach a maximum (14–15 atm) at ~90 °C, after which it began to decline. Representative results selected from the series of experiments are given in Table 1.

In order to determine the provisionally optimum conditions for this reaction, we first tested the conditions found for the synthesis of aryl vinyl ethers. In the KOH (50 mol%)/DMSO system at 120 °C for 3 h, phenols and naphthols reacted with acetylene forming aryl vinyl ethers in up to 80% yields.[15] When the reaction of aminophenol **1a** with acetylene was carried out under these conditions, a high rate of acetylene absorption was observed for 0.25 h: the pressure was grown to maximum value (~14.5 atm) and then abruptly dropped to 5.5 atm (see Figure 1, curve *1*). At this point, the yield of product **2a** did not exceed 28% and the reaction was accompanied by significant tar formation (see Table 1, entry 1). At lower temperatures (105 and 90 °C), vinyl ether **2a** was isolated in up to 45% yield although the volume of acetylene absorbed exceeded significantly its amount required by stoichiometry (see entries 2 and 3 and Figure 1, curve *2*).

Obviously, such a difference in the behavior of **1a** and the phenols and naphthols studied earlier[15] is due to the presence of a second nucleophilic center in the aminophenol molecule. Superbase medium KOH/DMSO (pK_a ~ 30–32)[17] would promote increase in the concentration of acetylenide anions and nucleophilicity of both centers (hydroxy and amino) capable of attacking a triple bond. More recently, it has been shown that the nucleophilic addition of arylamines to acetylene triggers the superbase-driven self-organization of three or four acetylene molecules with one arylamine molecule to 1-aryl-2,5-dimethylpyrroles[18(a)] or 1-aryl-3-ethyl-4-vinylpyrroles.[18(b)] Various combinations of nucleophilic addition to the triple bond and acetylene deprotonation was confirmed by quantum-chemical calculations.[19] In our case, similarly, the nucleophilic attack of the amino group of compound **1a** at the triple bond of acetylene also delivers a vinyl carbanion, which adds to the second acetylene molecule, thus propagating further oligomerization. This can cause formation of undesired oligomeric products.

In order to achieve full conversion of the starting aminophenol **1a** and acceptable yield of **2a**, the effects of base nature, H_2O content, temperature and time were tested. It was found that the additive of water (20 vol%) to the KOH/DMSO suppressed the tar formation. The acetylene absorption rate decreased in this case. However, at longer reaction duration (3 h), yield of vinyl ether **2a** reached 65% (see Table 1, entry 4 and Figure 1, curve *3*). The use of sodium hydroxide in aqueous DMSO (virtually, sodium aminopheolate) provided the synthesis of vinyl ethers **2a** in up to 77% yield (entries 5–10).

Screening of the reaction conditions showed that the best yield (77%) of vinyl ether **2a** was achieved when the reaction was run in the presence of sodium aminophenolate (*in situ* prepared from aminophenol and NaOH) at 90 °C for 3 h (see Table 1, entry 5 and Figure 1, curve *4*). At prolonged reaction time (to 4 h) and as well as augmented and diminished NaOH loading from 50 to 100 and 30 mol%, the yield of vinyl ether **2a** was lowered (entries 6–8). When the reaction was carried out at 80 °C, the yield of vinyl ether **2a** was reduced to 58% (entry 10). The LiOH/DMSO/H_2O system is less active as a catalyst in this reaction (entry 11). The optimum reaction conditions were extended over several aminophenols **1b–e** (Scheme 2).[†]



Scheme 2 *Reagents and conditions*: i, aminophenol **1** (50 mmol), NaOH (1.00 g, 25 mmol), DMSO (40 ml), H_2O (10 ml), initial pressure of acetylene at ambient temperature was ~14–16 atm, 90 °C, 3 h, 0.3 dm^3 steel stirred reactor. Isolated yields after distillation are given.

Under the above reaction condition, vinyl ether **2b** was prepared in 69% yield. The reaction of 4-aminophenol **1c** with acetylene gave vinyl ether **2c** in 85% yield. Vinyl ethers of *N*-alkyl- and *N*,*N*-dialkylaminophenols **2d**,**e** were also obtained in appropriate yields (72 and 62%, respectively). 4-Chloro-2-aminophenol and 5-nitro-2-aminophenol with electron-withdrawing substituents did not give even traces of the desired products (^{1}H NMR).

[†] *General procedure for the synthesis of vinyloxyanilines* **2**. A 300 ml pressure reactor equipped with a magnetic stirrer (250 rpm) was charged with sodium phenolate solution in aq. DMSO prepared by stirring a mixture of aminophenol **1** (50 mmol) and NaOH (1.00 g, 25 mmol) in DMSO (40 ml) and H_2O (10 ml) at room temperature for 0.5 h. The reactor was fed with acetylene and then decompressed to atmospheric pressure to remove air. The reactor was fed with acetylene again (initial pressure 14–15 atm) and heated under 90 °C for 3 h. After cooling to room temperature, the mixture was poured into ice water (100 ml) and extracted with diethyl ether (5×50 ml). The organic layers were combined, washed with H_2O (3×50 ml) and dried over $MgSO_4$. After evaporating diethyl ether, the residue was distilled *in vacuo* to give vinyl ether **2**.

In summary, we have developed an efficient procedure for the preparation of synthetically important vinyloxyanilines by direct vinylation of aminophenols with acetylene in the presence sodium aminophenolates in aqueous DMSO. The benefits of this method are use of available and cheap catalyst (less expensive than KOH-tailored ones), shorter reaction time and good yields.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2020.11.033.

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