

Potassium Hydroxide Catalyzed Addition of Arylamines to Styrenes

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Received 7 February 2011

Abstract: Potassium hydroxide is a competent and cheap catalyst for the intermolecular addition of arylamines to styrenes. The reactions are performed in nontoxic dimethyl sulfoxide and can be used for the large-scale synthesis of β -phenylethylamines.

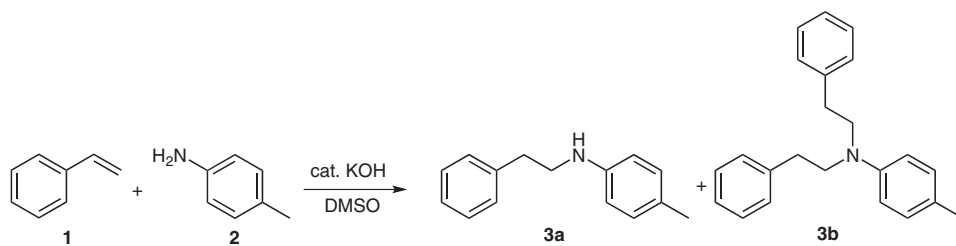
Key words: alkenes, amines, styrenes, potassium hydroxide, base-catalyzed hydroamination, β -phenylethylamines

During the last few years, many catalysts for the addition of N–H across carbon–carbon multiple bonds have been identified and used for a wide range of so-called hydroamination reactions.¹ However, most of these catalysts are expensive, air and moisture sensitive and therefore hardly feasible for industrial purpose. A more practicable and comparably cheap alternative is the base-catalyzed hydroamination.² Previous work has shown that comparatively strong bases such as *n*-BuLi, KO*t*-Bu, and CsOH or alkali metals such as sodium are able to deprotonate less basic amines to form the corresponding metal amides which can undergo nucleophilic addition to olefins.^{3,4} During our studies on inexpensive and practicable hydroamination catalysts, we found that even potassium hydroxide (KOH) is an appropriate strong base for this kind of reaction. Encouraged by this initial finding, we turned our attention towards the development of a KOH-catalyzed addition of arylamines to styrenes to obtain β -arylethylamines, which are of potential use as pharmaceuticals.^{3g,5} We performed the reactions in dimethyl sulfoxide (DMSO) because KOH is insoluble in most organic solvents (the solubility of KOH in DMSO at room temperature is 0.13 g/L).⁶ However, the solvent must be dried prior to use to avoid hydrolysis of the potassium amide intermediate formed from the corresponding amine and KOH. To remove the high-boiling DMSO at the end of the reaction the mixture was usually diluted with aqueous sodium hydroxide solution, and the products were simply extracted with dichloromethane.

Initial reactions were carried out in DMSO with equimolar amounts of styrene (**1**) and *p*-toluidine (**2**) with 2 mol% KOH at 60 °C for 18 hours in sealed Schlenk tubes. The regioselective addition of **1** to **2** led to the anti-Markovnikov product **3a** in 69% isolated yield (Table 1, entry 2). GC-MS-analysis showed that the dialkylated byproduct **3b** was also formed in trace amounts. Lower yields of **3a** were obtained when the reaction temperature was in-

creased to 80 °C or 110 °C (Table 1, entries 3 and 4), while keeping the temperature at 60 °C and varying the reaction time from 24 hours to 6 hours had only little effect on conversion and yield (Table 1, entries 2, 5–7). Interestingly, at room temperature, the dialkylated product **3b** was formed in an almost 1:1 ratio with **3a** (Table 1, entry 1). Further experiments with a 2:1 ratio of *p*-toluidine and styrene showed a maximum yield of 88% when the reaction was either performed at 60 °C for 6 hours or at 70 °C for 4 hours (Table 1, entries 8 and 11). Successive reduction of the excess of **2** at 70 °C (Table 1, entries 11–14) revealed that even with a 1.6:1 ratio of *p*-toluidine and styrene a comparably good yield of 82% could be obtained (Table 1, entry 12). Although reactions carried out so far have shown that a catalyst loading of 2 mol% is sufficient for good conversion, even 1 mol% KOH provided 71% isolated yield of **3a** (Table 1, entry 15). However, because of the low molecular mass of KOH, the catalyst loading was increased for practical reasons to 5 mol% for all further experiments. A corresponding reaction (Table 1, entry 16) gave **3a** with a slightly improved yield of 85%. Thus we used the conditions shown in Table 1, entry 16 for all further reactions.^{7,8}

Investigating the scope (see Table 2), we found that in the presence of 5 mol% KOH, *p*-toluidine also reacted with various substituted styrenes. The *para*-substituted styrenes 4-methylstyrene (**4**) and 4-*tert*-butylstyrene (**7**) gave slightly lower yields (72% and 69%) compared to nonsubstituted styrene (Table 2, entries 1, 2, and 5). In contrast to these results, the *ortho*-substituted styrenes **5** and **6** showed only low conversion with moderate to poor yields (Table 2, entries 3 and 4). A possible explanation for this observation is that the electron-donating effect of the alkyl groups destabilizes the negative charge formed at the benzylic position during the reaction. The addition of *p*-toluidine to the α -methylstyrene derivative **8** was also successful with a low yield of 19% (Table 2, entry 6). Even *trans*-stilbene showed some conversion with *p*-toluidine, albeit with very low yield of only 6% (Table 2, entry 8). Unfortunately, for these reactions, the reaction time had to be increased to 24 hours to achieve isolable yields. The same applies for the addition of **2** to allylbenzene (**9**) which probably proceeds through the isomerization of allylbenzene to the thermodynamically more stable β -methylstyrene (Table 2, entry 7). Further reactions of different primary and secondary amines with styrene have shown that arylamines are particularly suitable reaction partners. The addition of aniline (**11**) and donor-substituted *p*-anisidine (**13**) to **1** gave similar yields of 76% and 73%, re-

Table 1 Addition of *p*-Toluidine (**2**) to Styrene (**1**) in the Presence of Potassium Hydroxide

Entry	KOH (mol%)	Ratio styrene/ <i>p</i> -toluidine	Temp (°C)	Time (h)	Yield 3a (%) ^a
1	2	1:1	25	18	25 (23) ^b
2	2	1:1	60	18	69
3	2	1:1	80	18	63
4	2	1:1	110	18	46
5	2	1:1	60	24	72
6	2	1:1	60	12	70
7	2	1:1	60	6	62
8	2	1:2	60	6	88
9	2	1:2	60	4	69
10	2	1:2	60	2	52
11	2	1:2	70	4	88
12	2	1:1.6	70	4	82
13	2	1:1.4	70	4	79
14	2	1:1.2	70	4	77
15	1	1:1.6	70	4	71
16	5	1:1.6	70	4	85

^a Yields refer to isolated compound **3a**.

^b Isolated yield of compound **3b**.

spectively (Table 2, entries 9 and 11); whereas the less basic *p*-chloroaniline (**12**) showed only a moderate yield (52%, Table 2, entry 10). In this context, it must be noted that reaction of the comparatively acidic *p*-nitroaniline gave only trace amounts of the desired β -arylethylamine which could not be isolated. Unfortunately, no conversion was observed with alkylamines. With respect to the formation of the byproduct **3b** during the optimization reactions, we also used secondary arylamines in reactions with styrene. Fortunately, it turned out that the desired products were formed in moderate to good yields (Table 2, entries 14–17). However, the reaction of phenylhydrazine (**15**) gave the highest yield that was achieved during the entire study. NMR analysis and derivatization with acetophenone revealed that the alkylation proceeded at the aryl-bound nitrogen atom (Table 2, entry 13).

During our studies we also recognized that, in some reactions, a side product was formed which could be identified

as 3-phenylpropyl methyl sulfoxide (**36**). This byproduct is obviously formed by proton abstraction from DMSO and subsequent addition of the corresponding anion to styrene (Scheme 1).⁹ This competitive reaction is favored and occurs even at room temperature. Sulfoxide **36** was also observed during the reactions between styrene and *p*-toluidine at higher temperatures, which possibly explains the low isolated yields of **3a** (compare Table 1, entries 2–4). However, it might be possible that KOH first reacts with DMSO to form the corresponding anion which consequently then is responsible for amide formation.

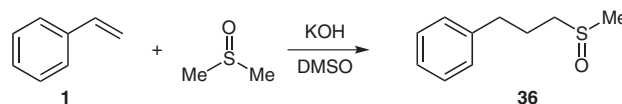
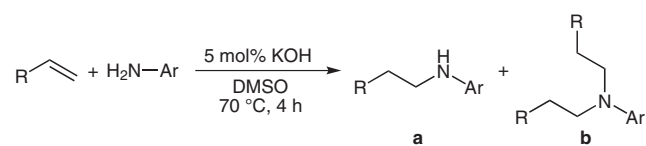
**Scheme 1** Side reaction of DMSO with styrene (**1**)

Table 2 Intermolecular Addition of Arylamines to Various Styrenes Catalyzed by Potassium Hydroxide

Entry	Alkene	Amine	Product	Yield (%) ^a
1				85
2				72
3				43
4				9
5				69
6				19 ^b
7				21 ^b
8				6 ^b
9				76
10				52

Table 2 Intermolecular Addition of Arylamines to Various Styrenes Catalyzed by Potassium Hydroxide (continued)

Entry	Alkene	Amine	Product	Yield (%) ^a
11				73
12				16
13				89 ^c
14				66
15				59
16				36
17				72

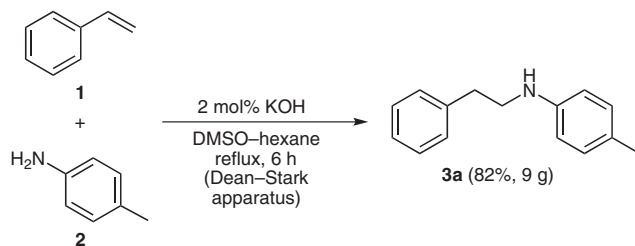
^a Reaction conditions: styrene (2.0 mmol), amine (3.2 mmol), KOH (0.1 mmol, 5 mol%), DMSO (1 mL), 70 °C, 4 h. Yields refer to isolated compounds.

^b The reaction time was 24 h.

^c Reaction conditions: styrene (2.0 mmol), hydrazine (3.2 mmol), KOH (0.04 mmol, 2 mol%), DMSO (1 mL), 70 °C, 4 h. Yields refer to isolated compounds.

Finally, we turned our attention towards the practical use of the KOH-catalyzed hydroamination reaction. All reactions described so far were performed in dry DMSO because water was inhibiting the potassium amide formation. Corresponding reactions in undried DMSO revealed no formation of the desired secondary amine. To avoid the drying of large quantities of DMSO, our idea was to conduct the reaction in a Dean–Stark apparatus. Therefore 50 mmol of freshly distilled styrene, commer-

cially available *p*-toluidine and undried DMSO were diluted with a 1:1 mixture of DMSO–hexane.¹⁰ After addition of 2 mol% KOH, the mixture was refluxed for 6 hours. To the resulting two-phase mixture a 1 M NaOH solution was added, and the aqueous phase was extracted with dichloromethane. The combined organic phases were dried, and the solvent was removed. The crude product was distilled in vacuum to produce **3a** in preparative useful quantities (9 g, 82%, Scheme 2).



Scheme 2 Practical example for the addition of *p*-toluidine (**2**) to styrene (**1**) using a Dean–Stark apparatus. *Reaction conditions:* styrene (50 mmol), *p*-toluidine (80 mmol), KOH (1 mmol), DMSO–hexane (1:1, 50 mL), 95 °C (oil bath), 6 h.

In summary, we have shown that KOH is a suitable catalyst for the addition of various arylamines to styrenes to produce pharmaceutically interesting β -arylethylamines. Various styrenes, primary and secondary arylamines, as well as phenylhydrazine could be converted into the corresponding products in moderate to good yields. Finally, we have shown that the KOH-catalyzed hydroamination is feasible for practical purposes without using Schlenk technique. For this purpose, commercially available starting materials and undried DMSO were used in a Dean–Stark apparatus with hexane as entrainer.

Acknowledgment

We thank the Deutsche Forschungsgemeinschaft for financial support of our research.

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- General Procedure Exemplified by the Reaction of Styrene (1) with *p*-Toluidine (2)**
An oven-dried Schlenk tube equipped with a Teflon stopcock and a magnetic stirring bar was transferred to a nitrogen-filled glove box and charged with *p*-toluidine (343 mg, 3.2 mmol), styrene (208 mg, 2.0 mmol), dry DMSO (1.0 mL), and KOH (99.99% from Sigma-Aldrich, 6 mg, 0.1 mmol, 5 mol%). The tube was sealed, and the resulting mixture was heated to 70 °C for 4 h. After the tube had been cooled to r.t. the reaction mixture was poured into an aq NaOH solution (1 M, 10 mL) and extracted with CH₂Cl₂ (3 × 10 mL). The combined organic layers were dried (MgSO₄) and concentrated under vacuum in the presence of Celite®. Finally, the crude product was purified by flash chromatography (light PE–EtOAc, 20:1) to give amine **3a** (359 mg, 1.7 mmol, 85%) as a pale yellow oil. ¹H NMR (500 MHz, CDCl₃): δ = 2.22 (s, 3 H), 2.86 (t, $J_{\text{H,H}}$ = 7.1 Hz, 2 H), 3.33 (t, $J_{\text{H,H}}$ = 7.1 Hz, 2 H), 3.46 (s, 1 H, NH), 6.51 (d, $J_{\text{H,H}}$ = 8.2 Hz, 2 H), 6.97 (d, $J_{\text{H,H}}$ = 8.0 Hz, 2 H), 7.16–7.23 (m, 3 H), 7.26–7.31 (m, 2 H) ppm. ¹³C NMR (126 MHz, DEPT, CDCl₃): δ = 20.3 (CH₃), 35.4 (CH₂), 45.3 (CH₂), 113.1 (CH), 126.3 (CH), 126.5 (C), 128.5 (CH), 128.7 (CH), 129.7 (CH), 139.3 (C), 145.7 (C) ppm. IR (neat): ν = 3404, 3025, 2918, 2861, 1615, 1519, 1318, 1259, 1182, 1080, 1031, 808, 699 cm⁻¹. HRMS (70 eV): *m/z* calcd for C₁₅H₁₇N: 211.1361; found: 211.1365.
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