

Selective Aromatic *N*-Substitution with *N*-(4-Tolyl)hydroxylamine by Addition of Polar Aprotic or Diethereal Solvent

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Amination of anisole and toluene with *N*-(4-tolyl)hydroxylamine in trifluoroacetic acid was tuned to regioselectively provide the corresponding diarylamine by partial replacement of trifluoroacetic acid with a polar aprotic or a diethereal solvent.

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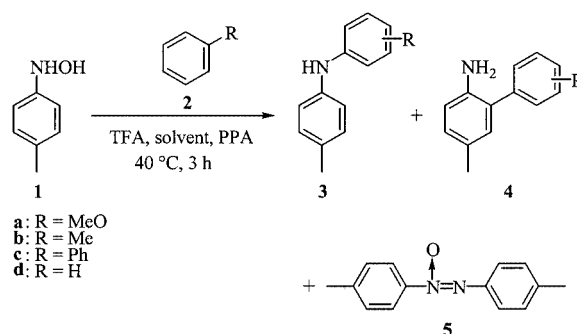
Introduction

Aromatic compounds are transformed to diarylamines by treatment with aryl azide^[1,2] or *N*-arylhydroxylamine.^[3,4] Recently, we tried to treat several aromatic compounds with *N*-arylhydroxylamine, including *N*-phenylhydroxylamine^[4] and *N*-(4-tolyl)hydroxylamine (**1**),^[5] in trifluoroacetic acid (TFA) in the presence of polyphosphoric acid (PPA) to produce the corresponding diarylamines by *N*-substitution as well as the corresponding aminobiphenyls by *C*-substitution. In these reactions, an arylnitrenium ion^[6,7] should be a reactive intermediate with a canonical resonance form^[8] wherein the positive charge populates carbon atoms of the ring and a nitrogen atom, and which then reacts with the aromatic compounds to give both the diarylamines and the aminobiphenyls.^[3,4] 4-(Nitro and cyano)phenylnitrenium ions^[2] from the corresponding aryl azides are efficiently capable of a selective aromatic *N*-substitution. Diarylamines were regioselectively formed in a case where electron-rich *N,N*-dimethylaniline was a nucleophile to arylnitrenium ion.^[9] We also found that anisole (**2a**) reacted with **1** to produce the corresponding diarylamine in a relatively high proportion, and came across the regioselective formation of the diarylamine by addition of 1,1,3,3-tetramethylurea (TMU) as a polar aprotic solvent. In this paper, we have

tuned the amination by the use of several solvents to regioselectively provide the corresponding diarylamine.

Results and Discussion

Compound **2a** reacted with **1** in a mixture of TFA and TMU containing PPA at 40 °C for 3 h to give *N*-(4'-tolyl)-2- and -4-anisidines (**3a**) and 2-amino-2'- and -4'-methoxy-5-methylbiphenyls (**4a**) accompanied by 4,4'-dimethylazoxybenzene (**5**) (Scheme 1).^[10] The replacement of TFA with TMU led to an increase in the yield of **3a** and a decrease in the yield of **4a** (Figure 1). For instance, with 30 % (v/v) TMU, compound **3a** was obtained selectively in 72% GLC yield (Table 1, Entry 2). The yield of **3a** then decreased as the proportion of TFA decreased.



Scheme 1

The replacement with polar aprotic solvents with a relatively high dielectric constant such as DMSO, 1,3-dimethyl-2-imidazolidinone (DMI), acetonitrile (AN) and propionitrile (PN) also led to an increase in the yield of **3a** and a decrease in the yield of **4a**, and brought about the regiose-

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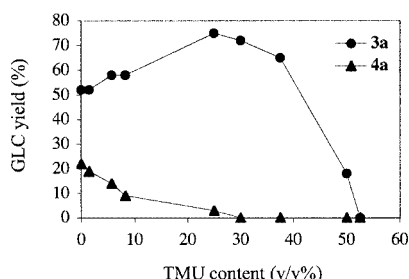

 Figure 1. Reaction of anisole (**2a**) with *N*-(4-tolyl)hydroxylamine (**1**) in a mixture of TFA and TMU

 Table 1. Reaction of anisole (**2a**) and toluene (**2b**) with *N*-(4-tolyl)hydroxylamine (**1**) in a mixture of TFA and a solvent

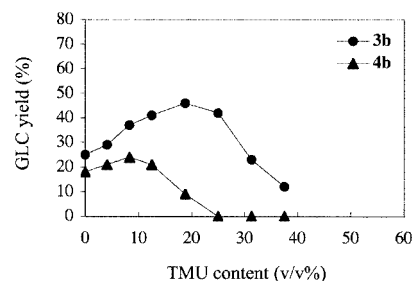
Entry ^[a]	Solvent	(v/v%)	2	GLC yield (%) ^[b]		
				3a ^[c]	4a ^[c]	5
1	—	—	2a	52 (7:93)	22 (19:81)	6
2	TMU	30	2a	72 (9:91)	0	25
3	DMSO	25	2a	63 (7:93)	0	18
4	DMI	31	2a	75 (3:97)	0	12
5	AN	63	2a	78 (3:97)	0	21
6	PN	50	2a	85 (6:94)	3 (0:100)	1
7	DME	38	2a	79 (7:93)	0	6
8	DO	25	2a	79 (9:91)	4 (0:100)	2
9	Hx	63	2a	44 (9:91)	2 (0:100)	31
				3b ^[c]	4b ^[c]	5
10	—	—	2b	25 (8:92)	18 (42:58)	10
11	TMU	25	2b	43 (13:87)	0	11
12	AN	50	2b	44 (15:85)	0	5
13	PN	50	2b	43 (12:88)	0	4
14	Hx	50	2b	24 (20:80)	15 (40:60)	13
				3c ^[c]	4c ^[c]	5
15 ^[d]	—	—	2c	0	28 (0:100)	7
16	PN	50	2c	19 (0:100)	0	12
				3d	4d	5
17 ^[d]	—	—	2d	2	25	6
18	PN	50	2d	trace	0	2

^[a] **1** (1.0 mmol), **2** (**2a**: 2.0 mL, 17.7 mmol; **2b**: 2.0 mL, 18.8 mmol; **2c**: 3.0 mmol; **2d**: 2.0 mL, 22.4 mmol), a mixture of TFA and a solvent (6.0 mL), PPA (1.2 mmol) at 40 °C for 3 h. ^[b] Based on **1**. ^[c] Also listed is the isomer ratio for *o/p* attack in parentheses. ^[d] The reaction using **2c** or **2d** was carried out at 20 °C.

lective formation of **3a** (Table 1, Entries 3–6); however, AN exerted its effect at 63 % (v/v) of the content (Entry 5). The replacement with 1,2-dimethoxyethane (DME) and 1,4-dioxane (DO), classified as a less polar aprotic solvent with a low dielectric constant, and hexane (Hx), a kind of nonpolar aprotic solvent, was also effective for the amination (Entries 7–9); however, Hx exerted its influence at 63 % (v/v) of the content (Entry 9).

The reaction of toluene (**2b**) with **1** was similarly carried out to produce 2,4'- and 4,4'-ditolylamines (**3b**) and 2-am-

ino-2',5- and -4',5-dimethylbiphenyl (**4b**) accompanied by **5** (Scheme 1). The replacement of TFA with TMU produced **3b** selectively when the content was 25 % (v/v) (Figure 2), and this also occurred with AN and PN at 50 % (v/v) of the content (Table 1, Entries 11–13). In this reaction, the replacement with Hx was unsuccessful for amination (Entry 14). These results indicate that a polar aprotic or a diethereal solvent might be effective for the amination.


 Figure 2. Reaction of toluene (**2b**) with *N*-(4-tolyl)hydroxylamine (**1b**) in a mixture of TFA and TMU

It is not completely clear what factors dictate the regiochemistry of the reaction with *N*-arylhydroxylamine, and the mechanism of the attack with the nitrogen atom has remained controversial. We suppose that the polar aprotic solvents might affect the initially formed arylnitrenium ion itself or the transition states,^[4] where the transition state in the *N*-substitution is more stabilized by solvation than that in the *C*-substitution due to the higher positive density of the former transition state, to allow the regiospecific attack by *N*-arylhydroxylamine on the aromatic compounds. The effect of nonpolar Hx on the selectivity of **3a** cannot be explained clearly at this stage, but seems to arise from the formation of nearly intimate ion pair with *N*-positive charge.

The order, **3a** (85%) > **3b** (43%) > **3c** (19%) > **3d** (trace), for the selective *N*-substitution using 50 % (v/v) PN (Table 1, Entries 6, 13, 16, 18) can be interpreted by the usual effect of the aromatic substitution. In the case where the total yield of **3–5** is markedly less than 100%, unidentified products (black tarry oil not being characterized) were probably formed by reaction with solvent and by uncertain reactions. The effect of solvent on the magnitude of the yield in *N*-selectivity and the solvent concentration for attaining the selectivity depend on the power of cationic solvation and the reactivity with solvent.

Conclusion

In summary, we have clarified that the partial replacement of TFA with a polar aprotic or a diethereal solvent brings about the amination of **2a** and **2b** with *N*-arylhydroxylamine to regioselectively produce the corresponding diar-

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- [10] Typical experimental procedure: *N*-(4-tolyl)hydroxylamine (**1**) (1.0 mmol) was added to a mixture of polyphosphoric acid (PPA, 1.2 mmol), anisole (**2a**) (2.0 mL, 17.7 mmol), TFA (3.6 mL) and TMU (2.4 mL) at 40 °C and stirred at that temperature for 3 h. After cooling to room temperature, the mixture was neutralized with aqueous Na₂CO₃ and extracted with dichloromethane (50 mL). The organic layer was separated, dried with anhydrous Na₂SO₄ and concentrated under reduced pressure. The resulting oil was analyzed by GLC to determine the yields of *N*-(4'-tolyl)-2- and -4-anisidines (**3a**), 2-amino-2'- and -4'-methoxy-5-methylbiphenyls (**4a**) and 4,4'-dimethylazoxybenzene (**5**). GLC yield: **3a** 72% (2-anisidine/4-anisidine = 9:91); **4a** 0%; **5** 25%. The oil was subjected to silica gel column chromatography with hexane and hexane/ethyl acetate as eluents to provide **3a** (129.0 mg, 60%, 2-anisidine/4-anisidine = 0:100) and a mixture of **3a** (2-anisidine/4-anisidine = 100:0) and **5** (18.1 mg, GLC ratio **3a**/**5** = 62:38).

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