Phase-Transfer Catalysis in the Ullmann Synthesis of Substituted Triphenylamines

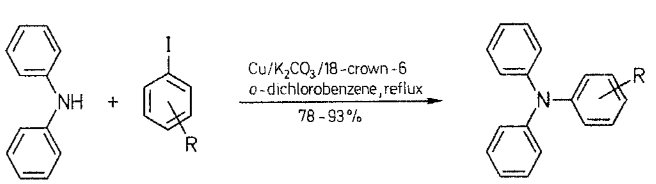
Sylvie Gauthier,* Jean M.J. Fréchet

Department of Chemistry, University of Ottawa, Ottawa, Ontario K1N 9B4, Canada

A variety of substituted triphenylamine derivatives were prepared in nearly quantitative yields by the use of 18-crown-6 as a phase transfer catalyst under the Ullmann reaction conditions.

The synthesis of triphenylamines substituted on one or more of the aromatic rings has traditionally been achieved by one of two different procedures. The first of these, direct substitution, has been used mainly for the introduction of bromo,[1] nitro,[2] or formyl[3] functionalities. Though satisfactory for the preparation of *p*-substituted products, this approach is not general and often leads to mixtures of mono-, di- and trisubstituted products. The second route, which has shown more versatility, is based on a procedure[4] that is essentially a modification of the Ullmann coupling of aryl halides.[5] In this process, a secondary amine is reacted with a substituted aryl halide to produce the desired triphenylamine derivative. The reaction is catalyzed by copper metal or copper bronze and requires temperatures around 200 °C. These reactions are thus conducted in high boiling solvents such as nitrobenzene or *o*-dichlorobenzene or without any solvent at all. Anhydrous potassium carbonate is added to the mixture to take up the hydrogen halide that is liberated. Best results are generally obtained with aryl iodides. In typical reactions,[6,7] with reaction times of 12–96 hours, yields vary from 40 to 80 % depending on the substrate chosen and the type of copper catalyst used.

As the desired reaction involves breaking the N–H bond of the secondary amine, it was thought that the reaction would proceed more easily if the anion of the amine could be used instead of the free amine. In view of the nature of the system, the best approach appeared to be the use of phase-transfer catalysis with 18-crown-6 as the catalyst and solid anhydrous potassium carbonate as the base, as shown in Scheme **A**.



1 **2a-h** **3a-h**

2, 3	R	2, 3	R
a	*o*-CH_3	**e**	*p*-OCH_3
b	*m*-CH_3	**f**	*o*-Cl
c	*p*-CH_3	**g**	*m*-Cl
d	*m*-OCH_3	**h**	*p*-Cl

Scheme **A**

Alternate approaches with quaternary ammonium or phosphonium salts did not appear to be feasible in view of the low thermal stabilities of these catalysts. Also, as maximum yields can only be obtained at fairly high temperatures, liquid-liquid phase-transfer catalysis cannot be of use. Finally, potassium carbonate is preferred over potassium hydroxide as a base because of the possibility of attack of the iodo substrate by the powerful hydroxyl ion.

As can be seen in Table 1, the presence of a phase-transfer catalyst increases considerably the yields of triphenylamine derivatives and decreases the reaction times quite substantially. As can be expected, however, this phase-transfer-catalytic process may not be used when base sensitive substituents are present. Thus, the reaction of diphenylamine with methyl 3-iodobenzoate only affords small amounts of triphenylamine, through copper catalyzed decarboxylation, and none of the desired substituted triphenylamine derivative.

Because of the very large increase in the rate of the reaction brought about by the addition of a phase-transfer catalyst, it was

Table 1. Ullmann Synthesis of Monosubstituted Triphenylamines According to Scheme **A** and of Di- and Trisubstituted Triphenylamines According to Scheme **B**

Product	R	Reaction Time (hours)	Yield (%)	m.p.[a] (°C)	Molecular Formula[b] or Lit. m.p. (°C)	Purification
3a	2-CH_3	18	92	58.5–60.51	56–58[8]	HPLC[c]
3b	3-CH_3	18	93	66–67	$C_{19}H_{17}N$ (259.4)	HPLC[c]
3c	4-CH_3	16	92	67.5–69	68–69[6]	HPLC[c]
3d	3-CH_3O	21	78[d]	oil	$C_{19}H_{17}NO$ (275.3)	HPLC[e]
3e	4-CH_3O	19	90	103–105.5	104[6]	recryst.[f]
3f	2-Cl	18	82	51–54	oil[8]	HPLC[c]
3g	3-Cl	21	87	87–88	$C_{18}H_{14}ClN$ (279.8)	recryst.[f]
3h	4-Cl	18	80	103–104.5	108–109[6]	recryst.[f]
5a	H	15	95	62–64	$C_{20}H_{19}N$ (273.4)	HPLC[c]
5b	CH_3	15	90	103–104.5	104–106[9]	recryst.[f]

[a] Uncorrected, measured on a Gallenkampf MF-370 apparatus.
[b] Satisfactory microanalyses obtained: C ±0.3, H ±0.3, N ±0.2, Cl ±0.02.
[c] Hexanes.
[d] Additional product isolated in impure form.
[e] 1% Ethyl acetate/99% hexanes.
[f] Ethanol.

Table 2. Ullmann Synthesis of 3-Methyltriphenylamine (**3b**) under Different Experimental Conditions

Catalyst[a]	Solvent	Reaction Time (hours)	Yield (%)	m.p. (°C)
Cu/18-crown-6	dichloromethane	18	0	
Cu/18-crown-6	toluene	48	< 10	
Cu/18-crown-6	chlorobenzene	36	54	67–68
Cu/18-crown-6	*o*-dichlorobenzene	18	93	66–67
Copper Bronze/ 18-crown-6	*o*-dichlorobenzene	24	85	65–66
Cu	*o*-dichlorobenzene	64	28	66–67
Copper Bronze	*o*-dichlorobenzene	64	74	67–68

[a] Cu refers to electrolytic copper.

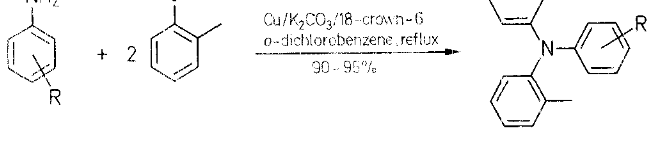
Table 3. Spectroscopic Data for Substituted Triphenylamines **3** and **5**

Product	IR (KBr or neat)[a] ν(cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS)[b] δ(ppm)
3a	2977, 2949, 1267	2.0 (s, 3H); 7.0 (m, 14H)
3b	2861, 1277	2.2 (s, 3H); 7.0 (m, 14H)
3c	2861, 1277	2.2 (s, 3H); 7.0 (m, 14H)
3d	2952, 2833, 1225, 1048	3.6 (s, 3H); 6.6 (m, 10H); 7.1 (m, 4H)
3e	2959, 2835, 1269, 1104	3.7 (s, 3H); 7.0 (m, 14H)
3f	1276, 1060	7.1 (m, 14H)
3g	1272	7.1 (m, 14H)
3h	1276, 1268	7.1 (m, 14H)
5a	2951, 2921, 1378, 1265, 1121, 1035	2.0 (s, 6H); 7.0 (m, 13H)
5b	2954, 2923, 1377, 1117, 1035	2.0 (s, 9H); 7.0 (m, 12H)

[a] Spectra recorded on a Nicolet FTIR MX-1 spectrophotometer.
[b] Spectra recorded on a Varian EM 360A spectrometer.

hoped that the reaction could be conducted in a lower boiling solvent, which would be more easily removed. Although a substantial amount of product (54%) is obtained in chlorobenzene after 36 hours, the use of the higher boiling *o*-dichlorobenzene is still preferred, as an almost quantitative yield (93%) is obtained in only 18 hours. As can be seen in Table 2, copper bronze used alone is much more effective than electrolytic copper as a catalyst, but is still very inferior to the combination of electrolytic copper with a phase-transfer catalyst.

Finally, disubstituted and trisubstituted triphenylamines have often been prepared by the reaction of aniline and a substituted aniline, respectively, with 2 moles of the desired substituted iodobenzene. The yields of such reactions generally vary between 40 and 70%. In view of the great improvement brought about by the use of a phase-transfer agent in the synthesis of monosubstituted triphenylamines, it was decided to apply these phase-transfer conditions to the preparation of the more highly substituted triphenylamines as shown in Scheme **B**. 2,2′-Dimethyltriphenylamine and 2,2′,2″-trimethyltriphenylamine were synthesized in 95% and 90% yields, respectively, (Table 3) confirming the general applicability of this method.



4a,b **2a** **5a,b**

4, 5	R
a	H
b	*o*-CH_3

Scheme **B**

Monosubstituted Triphenylamines 3; General Procedure:

Diphenylamine **1** (2 g, 11.8 mmol), a 1.5-fold excess of the desired iodocompound **2**, powdered anhydrous potassium carbonate (6.55 g, 47.4 mmol), electrolytic copper powder (1.5 g, 23.6 mmol) and 18-crown-6 (0.31 g, 1.17 mmol) are refluxed in *o*-dichlorobenzene (20 ml) under nitrogen until disappearance of the diphenylamine, as verified by TLC. The copper and inorganic salts are then removed by filtration of the hot reaction mixture. The solvent is distilled under reduced pressure and the residue freed from the crown ether and from most impurities by passing through a very short silica gel column. The triphenylamine derivative is then isolated by HPLC or by recrystallization. Specific details concerning the preparation of the different triphenylamine derivatives **3** are given in Table 1.

2,2′-Dimethyltriphenylamine (5a):

Freshly distilled aniline (**4a**; 65–66°C, 10 torr; 1 g, 10.7 mmol), *o*-iodotoluene (**2a**; 5.85 g, 26.8 mmol), powdered anhydrous potassium carbonate (11.88 g, 86.0 mmol), electrolytic copper powder (2.73 g, 43.0 mmol) and 18-crown-6 (0.57 g, 2.16 mmol) are refluxed in *o*-dichlorobenzene (20 ml) under nitrogen until disappearance of the aniline and the 2-methyldiphenylamine first formed, as verified by TLC. Upon completion of the reaction, the mixture is worked up following the procedure used for the monosubstituted derivatives.

2,2′2″-Trimethyltriphenylamine (5b):

This compound is prepared in the same fashion as 2,2′-dimethyltriphenylamine **5a**, but using distilled *o*-toluidine (**4b**; 85–87 °C, 14 torr; 1 g, 9.3 mmol) instead of aniline.

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