

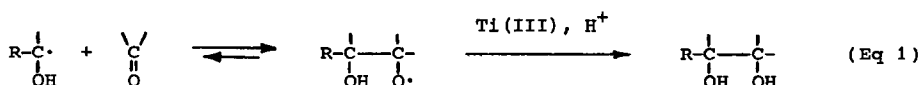
ARYLATIVE AMINATION OF ALDEHYDES PROMOTED  
 BY AQUEOUS TITANIUM TRICHLORIDE

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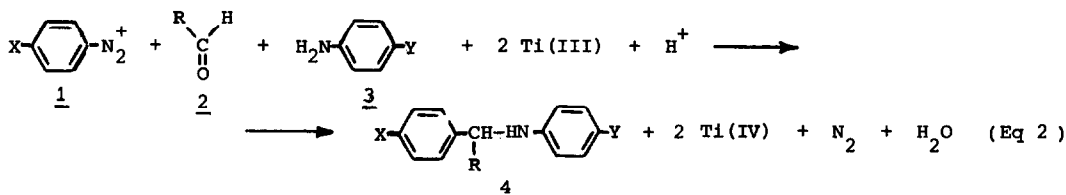
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Summary: Free-radical decomposition of arene-diazonium salts 1, catalyzed by aqueous  $TiCl_3$ , in the presence of aldehydes 2 and anilines 3 leads to secondary amines 4. A mechanism is proposed, according to which the aryl radical adds to the C-atom of the intermediate protonated imine.

Previous papers of our laboratory<sup>1</sup> have reported that the addition of ketyl radicals to C-atom of aldehydes and ketones, mediated by Ti(III) salts, is a synthetically useful process to vicinal diols since rapid reduction of the intermediate alkoxy radical by the metal ion makes the addition step practically irreversible (Eq 1).



Any further attempt to also promote the reductive arylation of carbonyls by reaction of aldehydes 2 with arene-diazonium salts 1, in the presence of Ti(III) ion, was unsuccessful. Nevertheless, when a primary aromatic amine 3 is added to the reaction mixture, arylation of the aldehyde occurs with replacement of the carbonyl O-atom by an amino and by an aryl group, according to Eq 2.



This reaction, which provides a new synthetic one-pot route to amines of type 4, is the subject of the present communication.

Conversions in which the O-atom of a carbonyl compound is directly replaced by others atoms are especially valuable for synthetic purposes, the Mannich reaction<sup>2</sup> and the Strecker synthesis<sup>3</sup> being two classical transformations of this type.

A typical procedure is as follows. Method A: the aryldiazonium salt 1 (0.01 mol, as chloride or fluoborate) is added in 20 minutes to a magnetically stirred solution of  $TiCl_3$  (0.022 mol, 15% commercially acidic aqueous solution), aldehyde 2 (from 0.01 to 0.10 mol) and aniline 3 (0.01 mol)

in glacial  $\text{CH}_3\text{COOH}$  (30 mL) and conc.  $\text{HCl}$  (2 mL). The reaction mixture is stirred at room temperature, under  $\text{N}_2$ , until the nitrogen evolution is ended (0.5-1 h). Method B: a cold solution of diazonium chloride 1 (10 mL, 1M) and a solution of 3 (0.01 mol) in  $\text{CH}_3\text{COOH}$  (10 mL) are added in 20 min. to a solution of  $\text{TiCl}_3$  (0.022 mol) and 2 (0.10 mol) in glacial  $\text{CH}_3\text{COOH}$  (20 mL) and conc.  $\text{HCl}$  (2 mL) at room temperature under  $\text{N}_2$ . Stirring is continued for 1 h. Isolated yields<sup>4</sup> (%) of amines 4, based on the starting 3, are collected in Table.

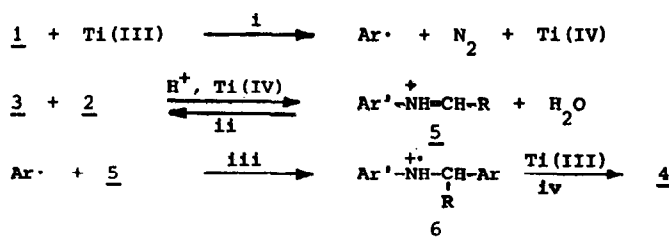
Table. Arylative Amination of Aldehydes by Arene-diazonium salts/ $\text{TiCl}_3$

Runs	X	Y	R <sup>a</sup>	Method	Yield (%) <sup>b</sup>	
					<u>4</u>	<u>7</u>
1	H	H	$\text{CH}_3$	A	50	34
2	H	H	$\text{CH}_3$	B	48	30
3	H	$\text{OCH}_3$	$\text{CH}_3$	A	58	36
4	H	$\text{OCH}_3$	$\text{CH}_3$	B	58	13
5	H	$\text{OCH}_3$	$\text{C}_2\text{H}_5$	A	40	24 <sup>e</sup>
6	H	$\text{OCH}_3$	p- $\text{CH}_3$ -Ph	A	35	- <sup>d</sup>
7	Cl	$\text{OCH}_3$	$\text{CH}_3$	A	60	10
8	$\text{CH}_3$	H	$\text{CH}_3$	A	48 <sup>e</sup>	44
9	$\text{OCH}_3$	H	$\text{CH}_3$	A	52 <sup>e</sup>	40

<sup>a</sup> Molar ratio 2:3 is 10:1 for  $\text{R}=\text{CH}_3$ , 5:1 for  $\text{R}=\text{C}_2\text{H}_5$  and 1:1 for  $\text{R}=\text{p-CH}_3\text{Ph}$ , respectively.

<sup>b</sup> Yield of isolated pure products, based on 3. <sup>c</sup> 15% of 2-ethyl-3-methyl-6-methoxyquinoline is isolated. <sup>d</sup> 16% of the corresponding imine is isolated. <sup>e</sup> Owing to the limited solubility of the diazonium salt, the reaction is performed at 45 °C.

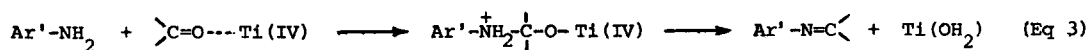
The reaction can be explained by the mechanism shown in Scheme 1.



The aryl radical, arising from the decomposition of the arene-diazonium salt induced by  $\text{Ti(III)}$  ion<sup>5</sup> (path i), adds to the C-atom of the protonated imine 5 (path iii). Further reduction of the resulting aminium radical 6, by a second  $\text{Ti(III)}$  ion (path iv), would afford 4.

Mechanistically, the first step of the reaction is the formation of the imine 5 (path ii) which, at the reaction pH, would be wholly protonated.

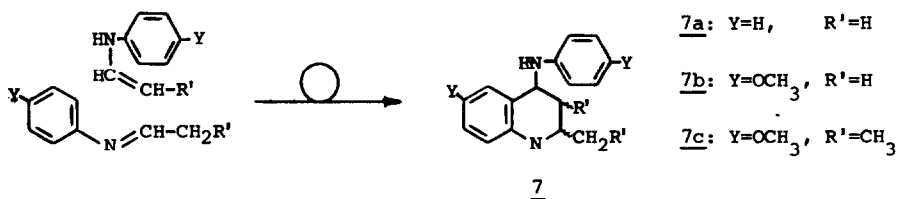
Condensation of amines with aldehydes is an equilibrium<sup>6</sup> and the reaction is usually carried out by refluxing the reagents with an azeotropic agent, separating the water as formed to shift equilibrium (path ii) to the right. The success of this transformation, under our reaction conditions (volume ratio H<sub>2</sub>O:CH<sub>3</sub>COOH, 1:1), may be attributed to the strong electrophilicity of Titanium ion towards the carbonyl oxygen<sup>7</sup> even in aqueous solution<sup>8</sup>. The coordination of Ti(III) or/and Ti(IV) ion<sup>9</sup> with the O-atom would prepare the carbonyl group towards attack by an amine, and the transfer of the carbonyl oxygen from carbon to Titanium<sup>10</sup> would favour the imine formation (Eq 3).



Addition of the aryl radical to 5 and reduction of 6 to 4 are two subsequent fast events that contribute to shift equilibrium of path ii to the side of 5.

Experimental evidence that the imine is a reaction intermediate is given by: a) isolation of the imine p-CH<sub>3</sub>-Ph-CH=N-Ph-OCH<sub>3</sub>-p in run 6, b) isolation of the "double Schiff's bases" 7a in runs 1, 2, 8 and 9, 7b in runs 3, 4 and 7, and 7c in run 5 (Table) as isomers mixture.

Formation of 7 involves the condensation of the enamine of 5 with 5 itself, according to the interpretation given by Forrest et al.<sup>11</sup> on the mechanism of the Doebner-Miller reaction<sup>12</sup> (Scheme 2).



While the yield of 7 depends on the order with which the reagents are mixed, the yield of 4 does not (Table, runs 1-4).

It should be emphasized that the addition of conc. HCl to the reaction mixture, by ensuring complete protonation of the imine, cleans up the reaction increasing the yield of 4.

This result stresses two peculiar features of the reaction: a) the affinity of the aryl radical<sup>13</sup> is higher towards the protonated than the unprotonated imino group<sup>14</sup>, and b) the aminium radical 6 is reduced by Ti(III) ion faster than the unprotonated amino radical, being the first by far more electrophilic than the latter. The faster the processes of paths iii and iv, the higher the yields of 4, because by-products, which may arise from either the imine and the aryl radical, are minimized.

Yields of 4 have not been optimized. Further investigation will hopefully broaden the scope of this new methodology and lead to elaboration of conditions under which the yields of 4 are improved.

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#### References and Notes

1. A. Clerici and O. Porta, *J. Org. Chem.*, 54, 3872 (1989) and references cited therein.
2. M. Tramontini, *Synthesis*, 703 (1973).
3. Th. Wieland in Houben-Weyl, *Methoden der Organischen Chemie*, XI/2, 305 (1958).
4. Secondary amines 4 are easily separated from the crude reaction mixtures, through an extraction with  $\text{CHCl}_3$ , as hydrochlorides complexed with Titanium ion. The free bases 4 are obtained after addition to the organic layers of a  $\text{Na}_2\text{CO}_3$  solution to a pH c.a. 9.
5. A.L.J. Beckwith and R.O.C. Norman, *J. Chem. Soc. B*, 402 (1969).
6. R.W. Layer, *Chem. Rev.*, 63, 489 (1963).
7. Ti(IV) ion has been shown to facilitate the formation of enamines and imines in anhydrous solvents. a) W.A. White and H. Weingarten, *J. Org. Chem.*, 32, 213 (1967); b) H. Weingarten, J.P. Chupp and W.A. White, *ibid.*, 32, 3246 (1967); c) M.C. Desai and P.F. Thadelo, *Tetrahedron Lett.*, 30, 5223 (1989).
8. Aqueous Ti(III) ion mediates the formation of cyclic acetals. A. Clerici and O. Porta, *Synth. Comm.*, 18, 2281 (1988).
9. In a blank reaction we have proved that an aqueous acidic solution of Ti(IV) is much more efficient than an aqueous acidic solution of Ti(III) ion in promoting imines formation.
10. The unusual nucleophilic substitution:  $\text{R-OH} + \text{Cl}^- \longrightarrow \text{R-Cl} + \text{OH}^-$  is catalyzed by Ti(III) ion which assists the departure of the OH group to which is already bounded or coordinated. A. Clerici, O. Porta and P. Zago, *Tetrahedron*, 42, 561 (1986).
11. T.P. Forrest, G.A. Dauphinee and W.F. Miles, *Can. J. Chem.*, 47, 2121 (1969).
12. Detailed studies of this reaction in the presence of Ti(IV) ion are underway.
13. The small nucleophilic character of the aryl radical would be revealed only in the presence of strong electron-deficient substrates. a) A. Clerici, F. Minisci and O. Porta, *Gazz. Chim. Ital.*, 103, 171 (1973); b) F. Minisci, E. Vismara, F. Fontana, G. Marini, M. Serravalle and C. Giordano, *J. Org. Chem.*, 51, 4411 (1986).
14. While the  $\text{>C=N-}$  group is less sensitive to polar effects than the  $\text{>C=O}$  group, being nitrogen less electronegative than oxygen, the  $\text{>C=N}^{\ddagger}$  group is more electrophilic than the  $\text{>C=O}$  group. W.P. Jencks, *Prog. Phys. Org. Chem.*, 2, 63 (1964).

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