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One-Pot Four-Component Reaction: Aqueous $TiCl_3/PhN_2^+$-Mediated Alkyl Radical Addition to Imines Generated in Situ

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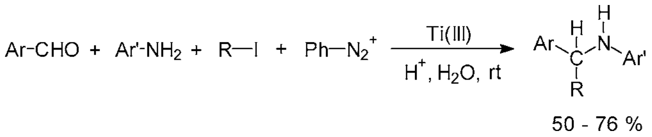
ABSTRACT



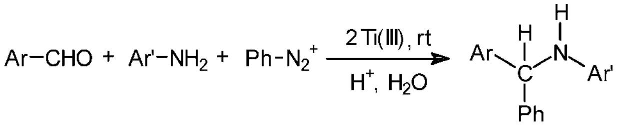
Ti(III)-induced free-radical decomposition of a phenyldiazonium salt, followed by phenyl radical iodine-atom abstraction from alkyl iodides, leads to a one-pot selective alkyl radical addition to the C-atom of imines generated in situ under aqueous acidic conditions.

The reaction of imines with organometallic reagents is a useful means to synthesize a variety of amines,[1] but these methods require strictly anhydrous conditions followed by tedious protection and deprotection steps. Synthetic applications of reductive alkyl radical addition to various C═N containing functional groups began to emerge only since 1980[2] and from then on have continued to increase.[3,4]

Among the C═N radical acceptors, oxime ethers, hydrazones, and glyoxylate imines are, by far, the most commonly used because simple imines are more prone to hydrolysis and have a slower radical addition rate,[5] due to lower electrophilicity, than the former substrates.

Nevertheless, in a previous paper[6] we reported that $TiCl_3$, under aqueous acidic conditions, promotes arylative amination of aldehydes in a one-pot, three-component reaction, according to Scheme 1.

Scheme 1



Titanium, owing to its reducing power in the Ti(III) state and to its Lewis acid character in the higher Ti(IV) state,[7] is

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[1] (a) Bloch, R. *Chem Rev.* **1998**, *98*, 1407−1438. (b) Denmark, S. E.; Nicaise, O. *Chem. Commun.* **1996**, 999−1004. (c) Saito, S.; Hatanaka, K.; Yamamoto, H. *Synlett* **2001**, 1859−1861 and references quoted herein.

[2] For reviews on radical addition to C═N bond, see: (a) Miyabe, H.; Ueda, M.; Naito, T. *Synlett* **2004**, 1140−1157. (b) Ishibashi, H.; Sato, T.; Ikeda, M. *Synthesis* **2002**, 695−713. (c) Friestad, G. K. *Tetrahedron* **2001**, *57*, 5461−5496. (d) Naito, T. *Heteocycles* **1999**, *50*, 505−541.

[3] (a) Yamada, K.; Fujihara, H.; Yamamoto, Y.; Miwa, Y.; Taga, T.; Tomioka, K. *Org. Lett.* **2002**, *4*, 3509−3511. (b) Yamada, K.; Yamamoto, Y.; Tomioka, K. *Org. Lett.* **2003**, *5*, 1797−1799 and references quoted therein. (c) Bertrand, M. P.; Coantic, S.; Feray, L.; Nougier, R.; Perfetti, P. *Tetrahedron* **2000**, 56, 3951−3961

[4] (a) Miyabe, H.; Ueda, M.; Nishima, A.; Naito, T. *Tetrahedron* **2004**, *60*, 4227−4235. (b) Miyabe, H.; Ueda, M.; Nishimura, A.; Naito, T. *Org. Lett.* **2002**, *4*, 131−134. (c) Miyabe, H.; Ueda, M.; Naito, T. *J. Org. Chem.* **2000**, *65*, 5043−5047. (d) Miyabe, H.; Ueda, M.; Yoshioka, N.; Yamakawa, K.; Naito, T. *Tetrahedron* **2000**, *56*, 2413−2420. (e) Miyabe, H., Yamakawa, K.; Yoshioka, N.; Naito, T. *Tetrahedron* **1999**, *55*, 11209−11218. (f) Miyabe, H.; Ueda, M.; Yoshioka, N.; Naito, T. *Synlett* **1999**, 465−467. (g) Halland, N.; Jorgensen, K. A. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1290−1295.

[5] Intramolecular 5-exo and 6-hexo cyclizations of imines are 1−2 orders of magnitude slower (10^5−10^6 s^{-1}) than hydrazones or oxime ethers (10^6−10^8 s^{-1}). Kim, S.; Yoon, K. S. *Tetrahedron* **1997**, *53*, 73−80.

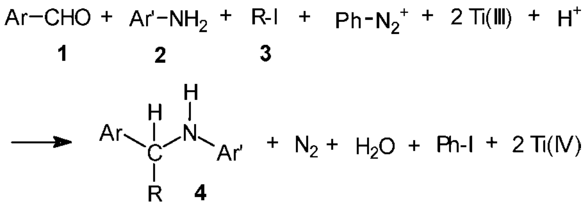
[6] Clerici, A.; Porta, O. *Tetrahedron Lett.* **1990**, *31*, 2069−2072.

10.1021/ol047595d CCC: $30.25

a highly specific reagent for promoting one-pot multistep chemical reactions, contributing to an overall synthetic efficiency from either ecological, economical, or practical points of view (no waste of solvents and TiO_2 results as the ultimate nontoxic metal residue).

Following this strategy, we now report that an aqueous acidic $TiCl_3$ solution promotes alkylative amination of aldehydes in a one-pot reaction involving up to four components, according to the stoichiometry of Scheme 2.

Scheme 2



$$\text{Ar-CHO} + \text{Ar}'\text{-NH}_2 + \text{R-I} + \text{Ph-N}_2^+ + 2\,\text{Ti(III)} + \text{H}^+ \longrightarrow \text{Ar-CH(R)-NH-Ar}' + \text{N}_2 + \text{H}_2\text{O} + \text{Ph-I} + 2\,\text{Ti(IV)}$$

When an alkyl iodide **3** is added to the reaction mixture of Scheme 1, selective alkyl radical addition to the C-atom of the imine generated in situ smoothly occurs, overcoming the competitive phenylation reaction.

The reactions were carried out by adding the phenyldiazonium salt (2.5−3.75 mmol), as the fluoroborate (method I) or as the chloride (method II), portionwise over 2 h at 20 °C to a solution containing **1** (2.5 mmol), **2** (3.75 mmol), **3** (7.5 mmol), and $TiCl_3$ (5.0−6.5 mmol of the 15% commercially aqueous acidic solution) in 15 mL of glacial acetic acid under N_2 atmosphere.

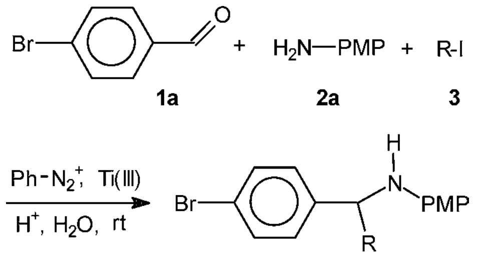
Workup, followed by purification, afforded the desired C-alkylated amines **4a**−**k** in fair to good yields, depending on the equivalents of phenyldiazonium and Ti(III) salts employed (Tables 1−3).

This simple one-pot selective alkylation would proceed by the sequence (i−v) indicated in Scheme 3.

The phenyl radical, arising from the Ti(III)-induced decomposition of the diazonium salt (path i),[8] generates an alkyl radical (path ii) by selective iodine-atom transfer. The alkyl radical adds to the C-atom (path iv) of the imine formed in situ[7] (path iii) and activated toward nucleophilic radical addition by either nitrogen protonation[9] or Ti(IV)−nitrogen complexation. The resulting electrophilic aminium radical **A**[10] is then readily reduced by a second equivalent of Ti(III) affording the final product **4** (path v).

Thus, this simple one-pot four-component method meets all the conditions required to make the synthesis successful and selective at the same time: (a) while titanium in its lower oxidation state acts both as radical initiator and radical terminator; in its higher oxidation state it plays the role of a Lewis acid complexing agent, providing imine formation and successive activation; (b) the iodine-atom transfer of path ii is responsible for the observed selectivity.

Table 1. Alkyl Radical Addition Reaction to an Equilibrium Mixture of **1a** and **2a** (Method I)[a]

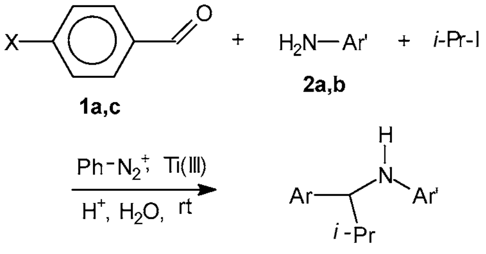


4a-e

entry	R	PhN_2^+	$TiCl_3$[b]	**4** yield[c] (%)
1	Me	1	2	**4a** (50)
2	Me	1	2	**4a** (55)[d]
3	heptyl	1	2	**4b** (56)
4	heptyl	1.5	2.3	**4b** (72)
5	isopropyl	1	2	**4c** (60)
6	isopropyl	1.5	2.3	**4c** (74)
7	isopropyl	1.5	2.6	**4c** (76)
8	cyclohexyl	1	2	**4d** (60)
9	*tert*-butyl	no reaction		
10	benzyl	1	2	**4e** (65)[e]
11	benzyl	1.5	2.6	**4e** (77)[e]
12	benzyl	1	2	**4ee** (82)

[a] Unless otherwise stated, the molar ratio of **1a**/**2a**/R−I was 1:1.5:3. [b] Equivalents of PhN_2^+ and of Ti(III) employed. [c] Yield of isolated product are based on the starting aldehyde; yields based on the converted aldehyde were always ≥90%. [d] Method II. [e] Molar ratio of **1a**/**2a**/benzyl iodide was 1:1.5:1.

Table 2. Isopropyl Radical Addition Reaction to an Equilibrium Mixture of **1a**−**c** and **2a**,**b** (Method I)[a]



4f-h

entry	**1**	X	**2**	Ar′	PhN_2^+	$TiCl_3$[b]	**4**	yield[c] (%)
1	**1b**	H	**2a**	PMP	1	2	**4f**	60
2	**1b**	H	**2a**	PMP	1	2	**4f**	62[d]
3	**1c**	Me	**2a**	PMP	1	2	**4g**	62
4	**1c**	Me	**2a**	PMP	1.5	2.6	**4g**	70
5	**1a**	Br	**2b**	*p*-tol	1	2	**4h**	56
6	**1a**	Br	**2b**	*p*-tol	1.5	2.6	**4h**	70

[a−d] See footnotes *a*−*d* of Table 1.

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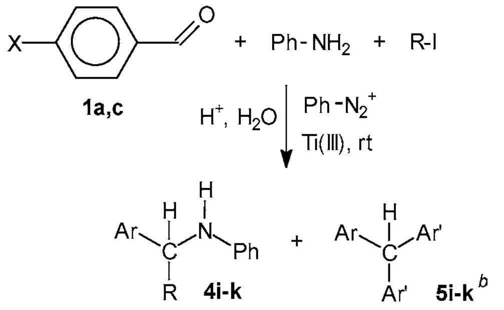
(7) Ti(IV) is known to promote imine formation. (a) Weingarten, H.; Chupp, J. P.; White, W. A. *J. Org. Chem.* **1967**, *32*, 3246−3249. (b) Desai, M. C.; Thadeio, P. F. *Tetrahedron Lett.* **1989**, *30*, 5223−5226. In a blank experiment we proved that an aqueous acidic solution of Ti(IV) is much more efficient than an aqueous acidic solution of Ti(III) in promoting imine formation.

(8) Beckwith, A. L. J.; Norman, R. O. C. *J. Chem. Soc. B* **1969**, 403−412.

(9) Under these reaction conditions (pH ≈ 1) the imine could be present either in its protonated form ($pK_a = 2.8$ in water for p-Cl-$C_6H_4CH{=}NHPh^+$) or as a N-Ti(IV)-complexed imine.

Table 3. Alkyl Radical Addition Reation to an Equilibrium Mixture of **1a**, **1c**, and Aniline (Method I)[a]



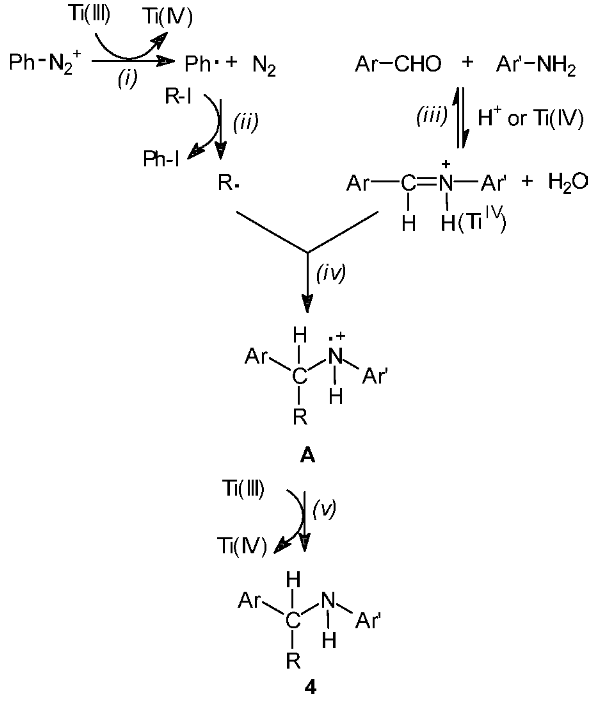
entry	**1**	X	R	**4**	yield[c] (%)	**5**	yield (%)
1	**1a**	Br	*i*-Pr	**4i**	45	**5i**	18[e]
2	**1c**	Me	*i*-Pr	**4j**	47	**5j**	15
3	**1a**	Br	cyclohexyl	**4k**	40	**5k**	18

[a] Molar ratio of **1**/$PhNH_2$/RI/PhN_2^+/$TiCl_3$ was 1:1.5:3:1:2. [b] Ar′ = *p*-C_6H_4NH-CH(R)Ar (see the Supporting Information). [c] See footnote *c* of Table 1. [d] Isolated yield based on the starting aldehyde; the effective molar yields of **5i**−**k** are one-third. [e] Preformed imine gave comparable yield of both **4i** and **5i**.

The reactions involving an iodine-atom transfer process from alkyl iodides to methyl or ethyl radicals, generated through organotin ($HSnR_3$) and/or triethylborane and alkyl zinc (Me_2Zn, Et_2Zn) mediators, has been largely utilized in the reductive alkylation of C═N activated substrates.[2−4]

However, the iodine-atom abstraction by the phenyl radical has thermodynamic and kinetic conditions much more favorable to be a very selective source of alkyl radicals. In fact, the equilibrium of path ii (Scheme 3) is completely shifted toward R• and its rate, close to the diffusion controlled limit ($k > 10^9$ M^{-1} s^{-1}),[11] is about 3 orders of magnitude higher than that of the iodine-atom abstraction by methyl radical ($k > 10^6$ M^{-1} s^{-1}).[12]

Scheme 3



In addition, all the alkyl radicals considered are more nucleophilic than the phenyl radical:[13] thus the phenyl radical iodine-atom abstraction, which is faster than the phenyl radical addition to a C═N bond, further contributes to practically eliminate the competitive phenylation (less than 5%).

By keeping the stationary concentration of the diazonium salt low during the reaction (e.g., slow addition) even the possible competitive alkyl radical addition to the diazonium group (diazocoupling)[14] was not operative.

In planning the synthesis, we first started with a favorable equilibrium of imine formation, selecting 4-Br-benzaldehyde **1a** and *p*-CH_3O-phenyl(PMP)amine[15] **2a**, as reactive partners. The reaction of these model substrates was investigated with various alkyl iodides **3** (R = methyl, heptyl, isopropyl, cyclohexyl, *tert*-butyl, and benzyl) and all of them, but *tert*-butyl, afforded the C-alkylated amines **4a**−**e** in fair to good isolated yields, depending on the equivalents of diazonium salt and $TiCl_3$ salt employed (Table 1).

A generalized improvement of ca. 15% yield was obtained by increasing the amount of diazonium salt from 1 to 1.5 equiv (entries 4, 7, and 11). The use of a preformed imine did not work better in term of product yields: in fact, under the conditions of entry 5 (Table 1) isopropyl radical addition to *N*-(4-bromobenzylidene)-4-methoxyaniline gave **4c** in 55% isolated yield.

The failure of *tert*-butyl radical to undergo C−C bond formation has to be ascribed to a steric hindrance experienced in the transition state[16] rather than to the reversibility of the addition step.[17] In fact, the benzyl radical, though more stable, enjoys less steric congestion around the radical center and afforded the higher yield of benzylated amine **4e**, even by using an equimolar amount of **1a** and benzyl iodide (entries 10 and 11).

It must be said that, under the experimental conditions adopted with the other alkyl iodides (e.g., 3 equiv of RI), **4e**

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(10) The aniline radical cation (pK_a = 7 in water) is a weaker acid than the anilinium (pK_a = 4.6 for $PhNH_3^+$) or phenylanilinium cations (RCH═$NHPh^+$), thus, at pH = 1, the equilibrium aminyl ↔ aminium radical, is by far shifted in favor of the latter. Russel, G. A.; Wang, L.; Rajaratnam, R. *J. Org. Chem.* **1996**, *61*, 8988−8991.

(11) (a) Kryeger, R. G.; Lorand, J. P.; Stevens, N. R.; Herron, N. R. *J. Am. Chem. Soc.* **1977**, *99*, 7589−7600. (b) Minisci, F.; Vismara, E.; Fontana, F. *J. Org. Chem.* **1989**, *54*, 5224−5227. (c) Minisci, F.; Vismara, E.; Fontana, F.; Morini, G.; Serravalle, M.; Giordano, C. *J. Org. Chem.* **1986**, *51*, 4411−4416.

(12) Hawari, J. A.; Kaminska, K. J. M.; Wayner, D. D.; Griller, D. *Substituent Effects in Radical Chemistry*; Viehe, H. G., Ed.; Reidel: D., Publishing Co: Dordrecht, 1986; p 81.

(13) (a) Clerici, A.; Minisci, F.; Porta, O. Gazz. *Chim. Ital.* **1973**, *103*, 171−178. (b) Minisci, F.; Porta. O. *Adv. Heterocycl. Chem.* 1**974**, *16*, 123−179.

(14) Minisci, F.; Coppa, F.; Fontana, F.; Pianese, G.; Zhao, L. *J. Org. Chem.* **1992**, *57*, 3929−3933.

(15) The PMP amine protecting group has been also chosen because it can be readily removed upon further CAN-oxidative transformations. Hasegawa, M.; Tanijama, D.; Tomioka, K. *Tetrahedron* **2000**, *56*, 10153−10158.

(16) This sensitivity to steric hindrance is in line with a crowded transition state due to Ti(IV) complexation rather than imine protonation.

was isolated only in trace amounts since it undergoes, during basic workup,[18] further N-benzylation with the excess of benzyl iodide, affording the undesired C- and N-dibenzylated product **4ee** in 82% isolated yield (entry 12).

To survey the scope and limitation of the present method, we next investigated the isopropyl radical addition to an equilibrium mixtures of **2a** with either benzaldehyde **1b** and *p*-tolualdehyde **1c** and of *p*-toluidine **2b** with *p*-Br-benzaldehyde **1a** (Table 2, entries 1−4 and entries 5, 6).

By comparing the yields of entries 1−4 of Table 2 with those reported in entries 5−7 of Table 1, it emerges that the addition reaction is relatively insensitive to substituent effects: the polarization of the C═N bond, induced by protonation or Ti(IV) complexation, overcomes the substituent effect on the aldehyde ring.

When aniline was used, as a partner of either **1a** or **1c** in the reactions with isopropyl and cyclohexyl iodide (Table 3), the yields of the expected **4i**−**k** were, disappointingly, low because of the concomitant formation of triarylmethane derivatives **5i**−**k**, which consumed 2 equiv of **4i**−**k** and 1 equiv of aldehyde. In a blank experiment we verified that the transformation occurs only in the presence of $TiCl_4$.[19]

The reaction can be generalized to an aliphatic aldehyde: under the standard conditions used for arylaldehydes (entry 1, Table 2), acetaldehyde afforded *N*-[2-(3-methyl)butane]-4-methoxyaniline **4m** in 50% isolated yield.

In conclusion, we believe that this selective alkyl radical addition to the C-atom of imines, performed in a one-pot four component reaction via the thermodynamically and kinetically most favored iodine-atom transfer from alkyl iodides, is a new subject of considerable interest having great practical and ecological advantages over methods involving toxic or expensive radical initiators.

Furthermore, preliminary experiments show that, by using the Ti(III)/PhN_2^+ system as a radical initiator, aminoalkylation of cyclic ethers and of cycloalkanes would be possible, due to hydrogen abstraction by the phenyl radical. Thus, efforts to extend the present method to both other sources of nucleophilic radicals and to other more activated C═N group acceptors are presently being made in our laboratory.

Acknowledgment. Financial support from MURST (Cofin 2002) is gratefully acknowledged. In addition, we thank Mr. M. Teti for running ^{1}H NMR analyses.

Supporting Information Available: Experimental section and full characterization data of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Bowman, W. R.; Clark, D. N.; Marmon, R. J. *Tetrahedron* **1994**, *50*, 1275−1294.

(18) Additional N-alkylation was not observed with the other more volatile and/or less reactive alkyl iodides. In fact, by extracting the reaction mixture with EtOAc prior to neutralization of the aqueous acidic solution, the C-alkylated products were isolated in their protonated form. Further concentration of the organic extracts, at a reduced pressure, allowed elimination of the excess RI, thus hampering the additional N-alkylation, which may occur during further basic workup.

(19) (a) Periasamy, M.; Jayakumar, K. N.; Bharathy, P. *J. Org. Chem.* **2000**, *65*, 3548−3550. (b) Yuan, Y.; Wang, X.; Li, X.; Ding, K. *J. Org. Chem.* **2004**, *69*, 146−149.