Pergamon

Tetrahedron Letters 43 (2002) 2785–2788

TETRAHEDRON
LETTERS

# Aromatization of enamines using the $TiCl_4/Et_3N$ reagent system[†]

Gadthula Srinivas and Mariappan Periasamy*

*School of Chemistry, University of Hyderabad, Central University PO, Hyderabad 500 046, India*

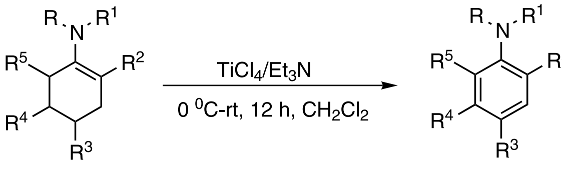
Received 21 November 2001; revised 7 February 2002; accepted 21 February 2002

**Abstract**—Aromatization of enamines to the corresponding aniline derivatives using the $TiCl_4/Et_3N$ reagent system is described.

$TiCl_4$ is one of the most widely used reagents in organic synthesis.[1] It has been used as a reagent for C–C bond forming reactions like the aldol condensation,[2] pinacol coupling,[3] Baylis–Hillman reactions,[4] and oxidative and reductive coupling reactions.[5] It is also useful in functional group transformations like the oxidation of propargylic alcohols to α,β-acetylenic aldehydes,[6] in conversion of acetals and ketals to carbonyl compounds,[7] tetrahydropyranyl ethers to acetates,[8] epoxides to vicinal halohydrin phosphates[9] and alkyl azides and ketones to amides,[10] the synthesis of functionalized 4,5-benzotropones[11] and enantiopure α-amino ketimines and aminoaziridines from 1-aminoalkyl chloromethyl ketones and different amines,[12] and the diastereoselective reduction of α-nitro ketones to *anti*-β-nitro alcohols.[13]

In recent years, there have been reports from this laboratory on synthetic applications of the $TiCl_4/Et_3N$ reagent system for the conversion of ketimines to pyrroles,[14a] trialkylamines and ketones to α,β-unsaturated aldehydes,[14b] the reductive coupling of aromatic aldehydes and imines to the corresponding diols and diamines,[14c] the conversion of 1-alkynes to diynes,[14d] *N*,*N*-dialkylarylamines to *N*,*N*,*N*,*N*-tetraalkylbenzidines,[14e] the enantioselective oxidative coupling of the chiral 1,1′-bi-2-naphthyl ester of phenylacetic acid,[14f] the synthesis of cyclobutanone derivatives via iminium ions,[14g] and the intramolecular reductive coupling of chiral diimines to chiral 3,4-disubstituted-2,5-diazabicyclo[4.4.0]decanes.[14h] In continuation of these efforts, we wish to report a simple convenient method for the conversion of enamines to the corresponding aromatic aniline derivatives using the $TiCl_4/Et_3N$ reagent system.

We have observed that enamines react with $TiCl_4/Et_3N$ at 0–25°C to give the corresponding aromatized products. (Eq. (1)).[15]



**1a-g** **2a-g** (1)

This transformation was found to be general for several enamines obtained from cyclohexanone derivatives and different secondary amines. The results are summarized in Table 1.

The enamine **1c** prepared from cyclohexanone and piperidine gave the corresponding aniline derivative **2c** in 75% yield. Also, the enamines obtained from α-tetralone and pyrrolidine **1b**, cyclohexanone and pyrrolidine **1e**, and 4-*t*-butyl cyclohexanone and pyrrolidine **1f** gave the corresponding ring aromatized products **2b**, **2e** and **2f** in 67–80% yields. Furthermore, the enamine obtained from cyclohexanone and *N*-methylaniline **1g**, yielded the aromatized product **2g** in 68% yield.

It was found that 2 equiv. of $TiCl_4$ are required for 1 equiv. of enamine in this transformation. However, the enamine of cyclohexanone and morpholine **1a**, and the 2-carboxycyclohexanone pyrrolidine enamine **1d** required 3 equiv. of $TiCl_4$ for optimum yields.

---

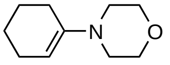
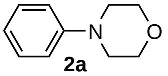
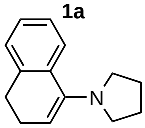
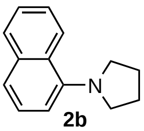
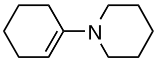
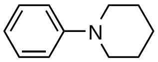
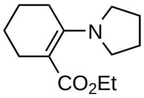
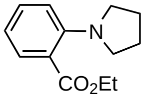
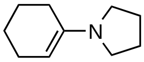
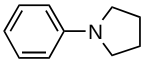
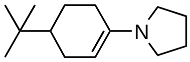
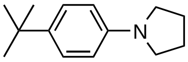
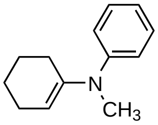
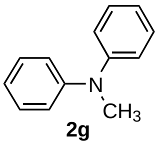
*Keywords*: enamines; dehydrogenation; aromatization; titanium tetrachloride.

* Corresponding author.

[†] Dedicated to Professor Herbert C. Brown on the occasion of his 90th birthday.

PII: S0040-4039(02)00380-5

**Table 1.** Reaction of enamines with the $Et_3N/TiCl_4$ reagent system

| Entry | Substrate | Product[a] | Yield[b]% |
|---|---|---|---|
| 1 | <br>**1a** | <br>**2a** | 84 |
| 2 | <br>**1b** | <br>**2b** | 80 |
| 3 | <br>**1c** | <br>**2c** | 75 |
| 4 | <br>**1d** | <br>**2d** | 74 |
| 5 | <br>**1e** | <br>**2e** | 72 |
| 6 | <br>**1f** | <br>**2f** | 67 |
| 7 | <br>**1g** | <br>**2g** | 68 |

[a] The products were identified using physical constants and the spectroscopic data[16] (IR, $^1H$ and $^{13}C$ NMR) and comparison with reported data.[19]

[b] Yields are based on the amount of enamine used.

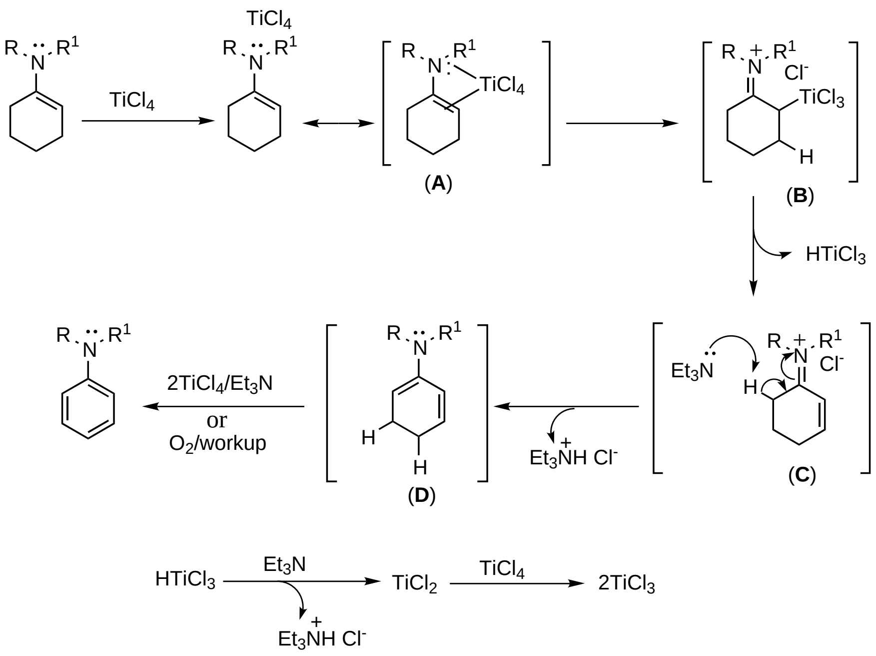
There have been reports that the enamines can be prepared through the reaction of ketones and an excess of the secondary amine using $TiCl_4$.[17] Accordingly, we have examined these transformations by preparation of the corresponding enamine in situ using α-tetralone, *N*-methylaniline, $Et_3N$ and $TiCl_4$ for further conversion to the aromatic amine using additional amounts of $TiCl_4/Et_3N$. However, in this reaction, only the corresponding enamine was isolated. Presumably, the enamine formed in situ maybe in a complexed form, which may not exhibit the same reactivity as free enamine towards $TiCl_4$ and $Et_3N$.

A tentative mechanism for the aromatization is outlined in Scheme 1. The $TiCl_4$ is expected to form a complex (**A**) through coordination of the enamine. Rearrangement of this complex would lead to the σ complex (**B**). The β-hydride elimination of this complex would give the α,β-unsaturated iminium ion intermediate (**C**) that upon further deprotonation would result in the dienamine (**D**). This intermediate upon a similar deprotonation–oxidation sequence of reactions could give the aromatized product. As the $TiCl_4/Et_3N$ reagent system is known to give the $TiCl_3$ species,[18] it was thought that 2 equiv. more of $TiCl_4/Et_3N$ would be required for aromatization. However, we have observed that there is no significant difference in yields when 2 equiv. or 4 equiv. of $TiCl_4/Et_3N$ are used. Presumably, further aromatization of the dienamine (**D**) takes place during work up via air oxidation.

Very recently, such aromatization of enamines was reported using palladium(II) salts in stoichiometric quantities.[19] Accordingly, the present transformation using the $TiCl_4/Et_3N$ reagent system is an attractive alternative method for such synthetic applications.

## Acknowledgements

We are grateful to the UGC and DST (New Delhi, India) for financial support. We are also thankful to the UGC for support under the Special Assistance Program.



**Scheme 1.**

## References

1. (a) Reetz, M. T. *Organotitanium Reagents in Organic Synthesis*; Springer: Berlin, 1986; (b) Mukaiyama, T. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 817.
2. (a) Crimmins, M. T.; King, B. W.; Tabet, E. A. *J. Am. Chem. Soc.* **1997**, *119*, 7883; (b) Crimmins, M. T.; Chaudhary, K. *Org. Lett.* **2000**, *2*, 775; (c) Han, Z.; Uehira, S.; Tsuritani, T.; Shinokubo, H.; Oshima, K. *Tetrahedron* **2001**, *57*, 987; (d) Harrison, C. R. *Tetrahedron Lett.* **1987**, *28*, 4135.
3. Tsuritani, T.; Ito, S.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **2000**, *65*, 5066.
4. (a) Shi, M.; Feng, Y. S. *J. Org. Chem.* **2001**, *66*, 406; (b) Kataoka, T.; Kinoshita, H.; Kinoshita, S.; Iwamura, T.; Watanabe, S. *Angew.Chem., Int. Ed. Engl.* **2000**, *39*, 2358; (c) Shi, M.; Jiang, J. K.; Cui, S. C.; Feng, Y. S. *J. Chem. Soc., Perkin Trans. 1* **2001**, 390; (d) Shi, M.; Jiang, J. K.; Feng, Y. S. *Org. Lett.* **2000**, *2*, 2397.
5. (a) Matsumara, Y.; Nishimura, M.; Hiu, H.; Watanabe, M.; Kise, N. *J. Org. Chem.* **1996**, *61*, 2809; (b) Kise, N.; Kumada, K.; Terao, Y.; Ueda, N. *Tetrahedron* **1998**, *54*, 2697; (c) Zhou, L.; Zhang, Y. *Tetrahedron* **2000**, *56*, 2953 and references cited therein.
6. Han, Z.; Shinokubo, H.; Oshima, K. *Synlett* **2001**, 1421.
7. Balme, G.; Gore, J. *J. Org. Chem.* **1983**, *48*, 3336.
8. Chandrashekar, S.; Ramachandar, T.; Venkat Reddy, M.; Takhi, M. *J. Org. Chem.* **2000**, *65*, 4729.
9. Ding, Y.; Hu, J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1651.
10. Desai, P.; Schildknegt, K.; Agrios, K. A.; Mossman, C.; Milligan, G. L.; Aube, J. *J. Am. Chem. Soc.* **2000**, *122*, 7226.
11. Langer, P.; Albrecht, U. *Synlett* **2000**, 526.
12. Concellon, J. M.; Bernard, P. L.; Riego, E.; Garcia-Granda, S.; Forcen-Acebal, A. *J. Org. Chem.* **2001**, *66*, 2764.
13. Ballini, R.; Bosica, G.; Marcantoni, E.; Vita, P. *J. Org. Chem.* **2000**, *65*, 5854.
14. (a) Periasamy, M.; Srinivas, G.; Bharathi, P. *J. Org. Chem.* **1999**, *64*, 4204; (b) Periasamy, M.; Bharathi, P. *Org.Lett.* **1999**, *1*, 857; (c) Periasamy, M.; Srinivas, G.; Karunakar, G. V.; Bharathi, P. *Tetrahedron Lett.* **1999**, *40*, 7577; (d) Periasamy, M.; Bharathi, P. *Organometallics* **2000**, *19*, 5511; (e) Periasamy, M.; Jayakumar, K. N.; Bharathi, P. *J. Org. Chem.* **2000**, *65*, 3548; (f) Periasamy, M.; Dharma Rao, V. *Tetrahedron: Asymmetry* **2000**, *11*, 1151; (g) Periasamy, M.; Jayakumar, K. N.; Bharathi, P. *Chem. Commun.* **2001**, 1728; (h) Periasamy, M.; Srinivas, G.; Suresh, S. *Tetrahedron Lett.* **2001**, *42*, 7123.
15. Typical experimental procedure: Dichloromethane (20 mL), the enamine (5 mmol) and $Et_3N$ (17 mmol) were taken under $N_2$. $TiCl_4$ (12 mmol 2.64 mL of a 1:1 solution of $TiCl_4/CH_2Cl_2$) in dichloromethane (10 mL) was added dropwise under $N_2$ at 0°C for 15 min. The reaction mixture was stirred for 0.5 h at 0°C and stirred further for 7–8 h at 25°C. It was quenched with saturated $K_2CO_3$ solution (15 mL). The organic layer was separated and the aqueous layer was extracted with dichloromethane (2×25 mL). The combined organic extract was washed with brine (10 mL) and dried over anhydrous $K_2CO_3$. The solvent was removed and the residue was chromatographed on a silica gel column using 0.5% EtOAc/hexane mixture as eluent.
16. Physical constants and spectroscopic data $^{13}C$ NMR (50 MHz, $CDCl_3$) for compounds **2a**–**2g**. Compound **2a**: mp 50–52°C (lit[7] 51–54°C), $^{13}C$ NMR ($\delta$ ppm) 49.44, 67.00, 115.80, 120.10, 129.25, 151.41. Compound **2b**: $^{13}C$ NMR ($\delta$ ppm) 24.90, 52.80, 111.61, 121.43, 124.36, 124.89, 125.60, 126.00, 128.35, 135.15, 147.86. Compound **2c**: $^{13}C$ NMR ($\delta$ ppm) 24.27, 25.60, 50.93, 116.72, 119.54, 129.10, 152.00. Compound **2d**: $^{13}C$ NMR ($\delta$ ppm) 14.37, 25.88, 50.80, 60.62, 114.00, 115.60, 117.66, 130.98, 131.63,

147.88, 169.02. Compound **2e**: $^{13}$C NMR ($\delta$ ppm) 25.44, 47.72, 111.83, 115.60, 129.15, 148.00. Compound **2f**: mp 40–41°C (lit 38–39°C), $^{13}$C NMR ($\delta$ ppm): 25.47, 31.64, 33.78, 47.94, 111.64, 125.95, 138.36, 145.84. Compound **2g**: $^{13}$C NMR ($\delta$ ppm): 40.27, 120.54, 121.33, 129.24, 149.18.

17. (a) White, W. A.; Weingarten, H. *J. Org. Chem.* **1967**, *32*, 213; (b) Carlson, R.; Nilsson, A.; Stromqvist, M. *Acta Chem. Scand. B.* **1983**, *37*, 7.
18. (a) Antler, M.; Laubengayer, W. A. *J. Am. Chem. Soc.* **1955**, *77*, 5250; (b) Fowles, G. W. A.; Hoodless, R. A. *J. Chem. Soc.* **1963**, 33.
19. Ishikawa, T.; Uedo, E.; Tani, R.; Saito, S. *J. Org. Chem.* **2001**, *66*, 186.