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# Microwave-promoted Trifluoroacetylation of Amines with $TiO(CF_3CO_2)_2$†

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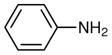
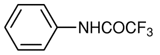
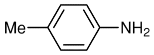
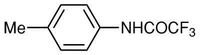
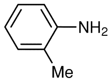
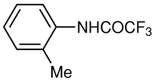
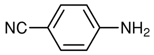
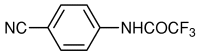
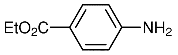
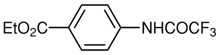
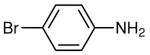
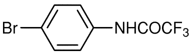
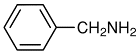
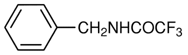
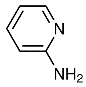
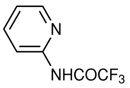
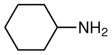
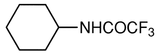
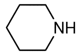
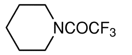
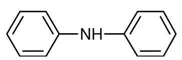
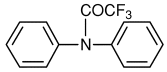
Conversion of amines to their corresponding trifluoroacetamides was performed with $TiO(CF_3CO_2)_2$ in a conventional microwave oven under solvent-free conditions in excellent yields.

Protection of primary and secondary amines is important in organic synthesis[1,2] due to their susceptibility to oxidation and replacement reactions. Conversion of amines into an amide is the most convenient and widely used method for protection of amino groups. In this respect, acetylation[1] and trifluoroacetylation[3–7] of amines have been the subject of many studies. Owing to the ease of removal, use of trifluoroacetyl as a protecting group has found wide applications in organic synthesis, especially for peptides,[8] aminosugars[9] and steroid glucosides.[10,11] The use of trifluoroacetic anhydride for conversion of amines to trifluoroacetamides, apart from the disadvantages of the low boiling point, volatility, and the corrosive and hygroscopic nature of trifluoroacetic anhydride, suffers also from generation of trifluoroacetic acid in the reaction mixture. In the course of our studies[12] on the reactions of $TiO(CF_3CO_2)_2$,[13] it was observed that $TiO(CF_3CO_2)_2$ can efficiently convert amines to their corresponding trifluoroacetamides using microwave irradiation. Owing to the difficulties of using of trifluoroacetic anhydride for acetylation reactions, we decided to study the applicability of $TiO(CF_3CO_2)_2$ as a highly stable solid, non-hygroscopic and new trifluoroacetylating agent for amines.

When we performed the reaction of aniline with $TiO(CF_3CO_2)_2$ under microwave irradiation in the absence of solvent, only 0.5 mol. equiv. of the reagent was required to give *N*-phenyltrifluoroacetamide in 95% yield after 5 min. Since the ratio of $TiO(CF_3CO_2)_2$ to amine in this reaction was 1:2, trifluoroacetic acid was produced and, instead, $TiO_2$ and water were formed in the reaction. Dramatic acceleration in the rate of reaction due to microwave irradiation was established in comparison with conventional heating. This reaction was completed at 100 °C in a sealed tube only after 48 h. We therefore studied the conversion of both primary and secondary amines to their corresponding trifluoroacetamides with this reagent under microwave irradiation. Different classes of amines were converted to their corresponding trifluoroacetamides with $TiO(CF_3CO_2)_2$ within 5–15 min in high to excellent yields. The results are shown in Table 1. In most cases, 0.5 mol. equiv. of the reagent was enough to complete the reaction, except in the cases of amines carrying electron-withdrawing groups (Table 1, entries 4–6) and diphenylamine (entry 11) which required 0.6–0.8 mol. equiv. of the reagent. Owing to the formation of $TiO_2$ in the reaction mixture, the mechanism in Scheme 1 is a possibility.

**Table 1** Microwave-assisted trifluoroacetylation of amines with $TiO(CF_3CO_2)_2$ under solvent-free conditions[a]

| Entry | Substrate | Product | Mol. equiv. of $TiO(CF_3CO_2)_2$ | *t* min | Yield (%)[b] |
|---|---|---|---|---|---|
| 1 |  |  | 0.5 | 5 | 97 |
| 2 |  |  | 0.5 | 6 | 96 |
| 3 |  |  | 0.5 | 6 | 94 |
| 4 |  |  | 0.8 | 15 | 85 |
| 5 |  |  | 0.6 | 15 | 86 |
| 6 |  |  | 0.7 | 10 | 90 |
| 7 |  |  | 0.5 | 5 | 93 |
| 8 |  |  | 0.5 | 6 | 98 |
| 9 |  |  | 0.5 | 5 | 97 |
| 10 |  |  | 0.5 | 10 | 88 |
| 11 |  |  | 0.7 | 15 | 60 |

[a]All reactions were performed with 700 W microwave energy. [b]Yield refers to isolated product.

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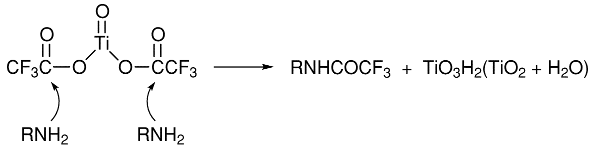
†This is a **Short Paper** as defined in the Instructions for Authors, Section 5.0 [see *J. Chem. Research (S)*, 1999, Issue 1]; there is therefore no corresponding material in *J. Chem. Research (M)*.



**Scheme 1**

In conclusion, owing to the stability, ease of preparation and handling and non-hygroscopic nature of $TiO(CF_3CO_2)_2$, this compound can be regarded as new bench top reagent for conversion of amines to trifluoroacetamides under neutral reaction conditions.

## Experimental

Products were characterized by their IR, NMR and mass spectral data or comparison with known samples. Infrared spectra were recorded on a Perkin Elmer 781 spectrometer. NMR spectra were recorded on a Bruker Avance DPX-250. Mass spectra were recorded on a Shimadzu GCMS-QP 1000 EX. The reactions monitoring was accomplished by TLC on silica gel polygram SILG/UV 254 plates or GLC on a Shimadzu GC-10A instrument.

*Typical Procedure for Microwave-assisted Trifluoroacetylation of Aniline with $TiO(CF_3CO_2)_2$.*—A mixture of aniline (1 mmol, 0.093 g) and $TiO(CF_3CO_2)_2$ (0.5 mmol, 0.145 g) was irradiated with microwaves (700 W) for 5 min. The residue was dissolved in $CH_2Cl_2$, dried with anhydrous sodium sulfate and filtered. The organic solvent was evaporated and the crude product was chromatographed on a short column of silica gel using $CCl_4$–$CH_2Cl_2$ (3:2) as eluent. Pure *N*-phenyltrifluoroacetamide was obtained in 97% yield (0.183 g).

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## References

1 J. F. W. McOmie, *Protective Groups in Organic Chemistry*, Plenum, London and New York, 1973.
2 T. W. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis*, Wiley, New York, 1991.
3 L. Kisfaludy, T. Mohacsi, M. Low and F. Drexler, *J. Org. Chem.*, 1979, **44**, 654.
4 A. G. M. Barrett and J. C. A. Lana, *J. Chem. Soc., Chem. Commun.*, 1978, **471**.
5 F. Kanai, T. Kaneko, H. Morishima, K. Isshiki, T. Takita, T. Takeuchi and H. Umezawa, *J. Antibiotics* (*Tokyo*), 1985, **38**, 39.
6 G. A. Dilbeck, L. Field, A. A. Gallo and R. J. Gargiulo, *J. Org. Chem.*, 1978, **43**, 4593.
7 D. D. Keith, J. A. Tortora and R. Yang, *J. Org. Chem.*, 1978, **43**, 3711.
8 F. Weygand and E. Frauendorefer, *Chem. Ber.*, 1970, **103**, 2437.
9 M. L. Wolfrom and H. B. Bhat, *J. Org. Chem.*, 1967, **32**, 1821.
10 H. Newman, *J. Org. Chem.*, 1965, **30**, 1287.
11 R. A. Lucas, D. F. Dickel, R. L. Dziemian, M. J. Ceglowski, B. L. Heusle and H. B. MacPhillamy, *J. Am. Chem. Soc.*, 1960, **82**, 5688.
12 N. Iranpoor and B. Zeynizadeh, *J. Chem. Res.* (*S*), 1998, 664.
13 P. Sartori, *Angew. Chem.*, 1964, **76**, 376.
14 A. Jacques and D. Claude, *Bull. Soc. Chim. Fr.*, 1975, 1933.