Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 21–23
Tetrahedron Letters

# Regioselective electrophilic trifluoromethylation of indolines, oxindoles and indoles in superacid

Sébastien Debarge, Kenza Kassou, Hélène Carreyre, Bruno Violeau, Marie-Paule Jouannetaud* and Jean-Claude Jacquesy

*Laboratoire 'Synthèse et Réactivité des Substances Naturelles', UMR 6514, 40, Avenue du Recteur Pineau, F-86022 Poitiers Cedex, France*

Received 9 September 2003; revised 23 October 2003; accepted 30 October 2003

**Abstract**—Treatment of indolines and *N*-acylindoles with $HF/SbF_5/CCl_4$ yields 6-trifluoro derivatives (indole numbering) whereas indoles and oxindoles give the 5-trifluoro derivatives in good yield.


Trifluoromethylation of aromatics may modify the physical and biological properties of such compounds, and the several approaches that have been developed to achieve this reaction have been reviewed.[1,2] Direct electrophilic trifluoromethylation can be carried out using trifluoromethyldibenzothiophenium salts and analogues[3,4] or carbon tetrachloride in the presence of HF and a Lewis acid.[5]

We have recently reported the regioselective electrophilic trifluoromethylation of substituted anilines and acetanilides in $HF/SbF_5$ in the presence of carbon tetrachloride.[6] Under the reaction conditions, the electrophile '$CCl_3^+$' obtained from $CCl_4$, reacts with the *N*- or *O*-protonated substrate, the halogen exchange being completed by treatment of the reaction mixture with HF/pyridine.

We report in this paper the electrophilic trifluoromethylation of indolines, oxindoles and indoles under similar conditions.[7]

The results reported in Tables 1 and 2 show that the reaction of indolines and indoles is regioselective. Indolines **1** and **3** which are *N*-protonated under the reaction conditions are trifluoromethylated at C-6, the alkyl group directing the substitution,[6] the poor electrophilic nature of $CCl_3^+$ ion accounting for the regioselectivity of the reaction. The efficient access to compound **2** should be compared to the previously reported five-step synthesis of this compound.[8] Indoline is thus a good precursor of the corresponding 6-trifluoromethyl-indole.[9]

On the other hand, oxindoles **5**, **6** and **9** selectively yield the corresponding 5-trifluoro derivatives **7**, **8** and **10**, respectively. An *O*-protonated amido group disfavours less this orientation and further reduces the influence of the C-3 methylene group as a directing group.[10] Oxindoles **7** and **8** have been previously prepared by total synthesis and evaluated as sleep inducers and tyrosine kinase inhibitors.[11]

Hydroxylation of indoles with $H_2O_2$ in superacids yields monohydroxy derivatives, substitution occurring on the benzene ring.[13] Under these conditions, indoles are protonated on the carbon atom of the pyrrole ring β to the nitrogen atom to yield iminium ions. Delocalization of the positive charge in the resulting ions accounts for the good reactivity of these substrates and for the poor regioselectivity observed in the electrophilic substitution. Whereas the reaction of indole **11** in superacids with $CCl_4$ led only to a complex mixture of polymers and of chloro and trifluoro derivatives, compounds **12** and **14a** gave the expected trifluoromethylated products **13** and **15a**, respectively, the intermediate iminium ions being more stabilized by the substitution at C-2 (Table 2).[14] The low reactivity of the trichloromethyl ion $CCl_3^+$ accounts for the selectivity of the reaction.

*Keywords*: Trifluoromethylation; Indolines; Indoles; Superacid.
* Corresponding author. Tel.: +33-5-49-45-37-02; fax: +33-5-49-45-35-01; e-mail: marie.paule.jouannetaud@univ-poitiers.fr

0040-4039/$ - see front matter © 2003 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2003.10.192

**Table 1.** Trifluoromethylation of indolines and oxindoles

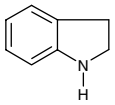
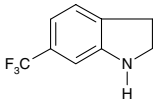
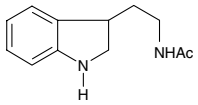
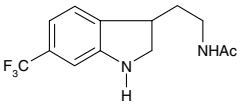
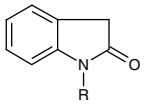
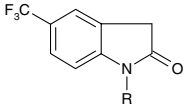
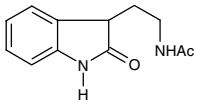
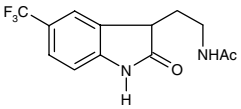
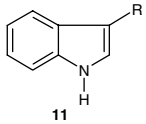
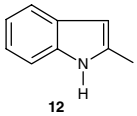
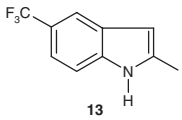
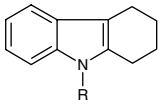
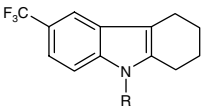
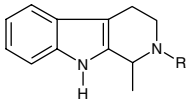
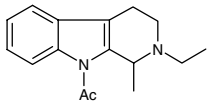
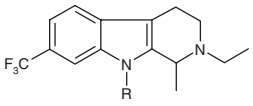
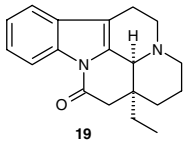
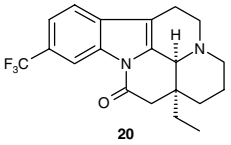
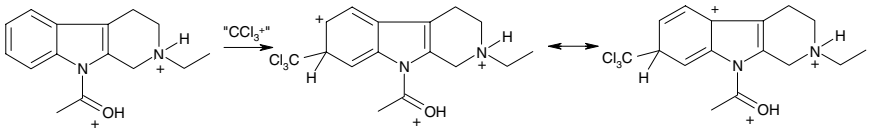
| Substrate | Product | Reaction time (h) | Temperature (°C) | Yield (%) |
|---|---|---|---|---|
|  **1** |  **2** | 1.5 | 0 | 83 (Ref. 8) |
|  **3** |  **4** | 2 | −20 | 80 (Ref. 12) |
|  **5** R = H<br>**6** R = $CH_3$ |  **7** R = H<br>**8** R = $CH_3$ | 2 | 0 | **7** 30 (Ref. 11a)<br>**8** 50 (Ref. 11b) |
|  **9** |  **10** | 2 | 0 | 50 (Ref. 12) |

**Table 2.** Trifluoromethylation of indole derivatives

| Substrate | Product (%) | Reaction time (h) | Temperature (°C) | Yield (%) |
|---|---|---|---|---|
|  **11** R = H or $CH_3$, $CH_2CH_2NHAc$ | Degradation products | 0.25 | −20 | — |
|  **12** |  **13** | 0.25 | −20 | 60 (Ref. 14a) |
|  **14a** R = H<br>**14b** R = Ac |  **15a** R = H<br>No reaction | 0.5<br>0.5 | −20<br>−20 | 65 (Ref. 14b)<br>— |
|  **16** R = H, $COCH_3$, $C_2H_5$ | No reaction | 0.5 | 0 | — |
|  **17** |  **18a** R = Ac<br>**18b** R = H | 0.5 | −20 | **18b** 53 (Ref. 12) |
|  **19** |  **20** | 0.5 | −20 | 50 (Ref. 12) |



**Scheme 1.**

It should be pointed out that compound **14b** is unreactive, the diprotonation at the carbonyl group and at the carbon atom α to nitrogen deactivating this compound.

Surprisingly, tetrahydrocarbolines **16** are unreactive under the reaction conditions, the possible diprotonation on both nitrogen atoms perhaps making the substitution very difficult. On the other hand, the *N*-acetyl derivative **17** yields trifluoro derivative **18a** which is deacetylated to **18b**.[15] This result can be explained by the *O*-protonated enamide system being less deactivating than the protonated indole nucleus. Trichloromethylation *meta* to the nitrogen atom leads through a stabilized intermediate to the product **18a** (Scheme 1).

This reaction has been successfully applied to the trifluoromethylation of vinburnine CERVOXAN® **19**, a vasodilator, to its analogue **20**.

To conclude, it should be pointed out that the reported reaction constitutes an efficient and convenient access to trifluoromethylated indoles either directly from substituted indoles to give the 5-trifluoro derivatives, or by reacting indolines, followed by aromatization to give the 6-trifluoro analogues.

## Acknowledgements

We thank CNRS and Ligue Nationale contre le Cancer (Comité de Charente Maritime) for financial support and Région Poitou-Charentes for a grant (to S.D.).

## References and Notes

1. McClinton, M. A.; McClinton, D. A. *Tetrahedron* **1992**, *48*, 6555–6666, and references cited therein.
2. Langlois, B. R.; Billard, T. *Synthesis* **2003**, 185–194.
3. Umemoto, T.; Ishihara, S. *Tetrahedron Lett.* **1990**, *31*, 3579–3582.
4. Yang, J. J.; Kierchmeier, R. L.; Schreeve, J. J. *J. Org. Chem.* **1998**, *63*, 2656–2660.
5. (a) Benning, A. F.; Gottlieb, H. B. U.S. Patent 2,273,922, 1942; *Chem. Abstr.* **1942**, *36*, 3812; (b) Opie, T. R. U.S. Patent 4,207,266, 1980; *Chem. Abstr.* **1980**, *93*, 167863r; (c) Marhold, A.; Klauke, E. Gen Offen. DE 2928745, 1981; *Chem. Abstr.* **1981**, *94*, 192005r; (d) Marhold, A.; Klauke, E. *J. Fluorine Chem.* **1981**, *18*, 281–291; (e) Desbois, M. Fr. Demande FR Patent 2538380, 1985; *Chem. Abstr.* **1985**, *102*, 61914x; (f) Nasu, R.; Shigehara, I.; Kawashima, J.; Maeda, M. Eur. Patent Appl. EP 137424, 1985; *Chem. Abstr.* **1985**, *103*, 104684n.
6. Debarge, S.; Violeau, B.; Bendaoud, N.; Jouannetaud, M. P.; Jacquesy, J. C. *Tetrahedron Lett.* **2003**, *44*, 1747–1750.
7. Typical experiment: To HF (6 mL) and $SbF_5$ (3 mL) at −20 °C in a Teflon reactor, the substrate (2 mmol) then $CCl_4$ (0.58 mL, 3 equiv) were successively added. The mixture was maintained at a given temperature for 0.25–2 h, according to the substrate (see Table 1). The mixture was then cooled to −78 °C and HF/pyridine 70:30 (v/v) (2 mL) was added. The reaction mixture was kept at 0 °C overnight, then very carefully poured into a vigorously stirred mixture of $Na_2CO_3$, $H_2O$ and ice. After extraction with ethyl acetate (three times) and usual work-up, the reaction mixture was evaporated to dryness and purified on $SiO_2$.
8. (a) Tischler, A. N.; Lanza, T. J. *Tetrahedron Lett.* **1986**, *27*, 1653–1656; (b) Bromidge, S. M.; Dabbs, S.; Davies, D. T.; Duckworth, D. M.; Forbes, I. T.; Ham, P.; Jones, G. E.; King, F. D.; Saunders, D. V.; Starr, S.; Thewlis, K. M.; Wyman, P. A.; Blaney, F. E.; Naylor, C. B.; Bailey, F.; Blackburn, T. P.; Holland, V.; Kennett, G. A.; Riley, G. J.; Wood, M. D. *J. Med. Chem.* **1998**, *41*, 1598–1612.
9. Kametani, T.; Tetsuji, O.; Tatsuschi, I. M. *J. Chem. Soc., Perkin Trans. 1* **1981**, 290–294.
10. Berrier, C.; Jacquesy, J. C.; Jouannetaud, M. P.; Morellet, G. *Bull. Soc. Chim. Fr.* **1986**, 158–164.
11. (a) Hardtmann, G. E.; Schilling, U.S. Patent 4,160,032, 1979; *Chem. Abstr.* **1979**, *91*, 107890; (b) Rewcastle, G. W.; Palmer, B. D.; Dobrusin, E. M.; Fry, D. W.; Kraker, A. J.; Denny, W. A. *J. Med. Chem.* **1994**, *37*, 2033–2042.
12. All new compounds have been characterized by $^1H$, $^{13}C$ NMR and HRMS (EI). Selected data: Compound **4**: $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.17 (d, $J = 7.7$ Hz, H-4), 6.96 (d, $J = 7.7$ Hz, H-5), 6.88 (s, H-7); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 130.4 (q, $^2J_{CF} = 31$ Hz, C-6), 126.2 (q, $^1J_{CF} = 282$ Hz, $CF_3$), 115.5 (q, $^3J_{CF} = 4$ Hz, C-5), 105.6 (q, $^3J_{CF} = 3.8$ Hz, C-7); MS $C_{13}H_{15}N_2OF_3$: calcd 272.1137, found 272.1142; Compound **10**: $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.55 (br s, H-4), 7.48 (br d, $J = 8.2$ Hz, H-6), 6.98 (d, $J = 8.2$ Hz, H-7); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 125.7 (q, $^3J_{CF} = 3.8$ Hz, C-4), 124.5 (q, $^2J_{CF} = 32.4$ Hz, C-5), 124.3 (q, $^1J_{CF} = 267$ Hz, $CF_3$), 121.0 (q, $^3J_{CF} = 3.8$ Hz, C-6); MS $C_{13}H_{13}F_3N_2O_2$: calcd 286.1055, found 286.1045; Compound **18b**: $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.59 (br s, H-8), 7.49 (d, $J = 8.2$ Hz, H-5), 7.28 (br d, $J = 8.2$ Hz, H-6); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 122.1 (q, $^1J_{CF} = 270$ Hz, $CF_3$), 119.3 (q, $^2J_{CF} = 31.7$ Hz, C-7), 115.9 (q, $^3J_{CF} = 4.9$ Hz, C-6), 108.4 (q, $^3J_{CF} = 4.9$ Hz, C-8); MS $C_{15}H_{17}N_2F_3$: calcd 282.1344, found 282.1371; Compound **20**: $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 8.65 (s, H-16), 7.51 (s, H-13, H-14); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 126.5 (q, $^2J_{CF} = 32.2$ Hz, C-15), 124.7 (q, $^1J_{CF} = 272$ Hz, C-22), 120.7 (q, $^3J_{CF} = 3.7$ Hz, C-14), 113.5 (q, $^3J_{CF} = 4.1$ Hz, C-16); MS $C_{20}H_{21}N_2OF_3$: calcd 362.1606, found 362.1598.
13. Berrier, C.; Jacquesy, J. C.; Jouannetaud, M. P.; Renoux, A. *New J. Chem.* **1987**, *11*, 611–615.
14. (a) Hary, U.; Roettig, U.; Paal, M. *Tetrahedron Lett.* **2001**, *42*, 5187–5189; (b) Forbes, E. J.; Stacey, M.; Tatlow, J. C.; Wragg, R. T. *Tetrahedron* **1960**, *8*, 67–72.
15. The compound **18a** is unstable and decomposed rapidly to give the compound **18b**.