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Nucleophilic addition of $TMSCCl_3$ to *N*-phosphinoyl benzaldimines: a route to *N*-phosphinoyl-α-(trichloromethyl)benzylamines

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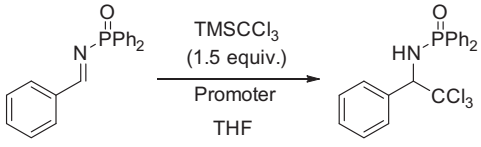
ABSTRACT

Nucleophilic addition of readily available $TMSCCl_3$ to *N*-phosphinoyl benzaldimines allows preparation of *N*-phosphinoyl-α-(trichloromethyl)benzylamines. Typically, the reaction in THF at room temperature using tetrabutylammonium difluorotriphenylsilicate (TBAT) as a catalytic promoter, afforded very good yields (65–95% range) for most derivatives within 1 h at room temperature.

α-Trichloromethylamines are interesting biologically active compounds used as: herbicides,[1] insecticides[2] or fungicides,[3] and more recently have revealed dopaminergic neurotoxicity properties.[4] They also represent a key intermediate in the synthesis of valuable organic molecules such as, α,α-dichloroimines[5] and α-trichloromethyl imines,[6] 2,2-dichlorovinylamines and (2-chloroethynyl)amines[7] and 2,2-dichloroaziridines[7,8] and enamino esters.[9] α-Trichloromethylamines are directly synthesised by nucleophilic addition of a trichloromethyl anion equivalent to an imine. A few different sources of CCl_3^- can be used: trichloroacetic acid,[10] chloroform[8,11] or trimethyl(trichloromethyl)silane.[12] Use of trichloroacetic acid is limited by harsh decarboxylation conditions while the use of $CHCl_3$ requires strong bases (*t*-BuOK and NaHMDS). Conversely, $TMSCCl_3$ only requires activation by a silylphilic promoter, typically a fluoride ion. Following our recent improvements on the synthesis of $TMSCCl_3$ (70% isolated yield),[13] we aimed to extend the use of this reagent to imines. Present nucleophilic reactions of $TMSCCl_3$ with imines are limited to very few examples: a low yielding (34%) 1,2-addition to a salicylaldimine, using an intramolecular activation of the imine through chelation of boron trifluoride etherate with the adjacent hydroxyl group,[12a] and Li's diastereoselective addition of $TMSCCl_3$ to *N*-(*tert*-butylsulfinyl)aldimines.[12b,c] We conceived that unprecedented nucleophilic addition of $TMSCCl_3$ to diphenylphosphinoyl benzaldimines would be an efficient route to useful *N*-phosphinoyl-α-(trichloromethyl)benzylamines.

We initially investigated the nucleophilic reaction of $TMSCCl_3$ with (*E*)-*N*-benzylidene-*P*,*P*-diphenylphosphinic amide (**1a**) (Table 1). Initial trials revealed that $TMSCCl_3$ requires activation by a silylphilic promoter; the fluoride ion from TBAT (tetrabutylammonium difluorotriphenylsilicate) was most effective here (run 1 vs run 2). Further investigation showed that the reaction could be efficiently carried out in THF at room temperature within an hour, using only 1 mol % of TBAT (run 2 vs runs 3 and 4). Insoluble CsF was poorly effective (run 5). The diphenylphosphinoyl benzaldimine starting materials **1** are accessed by titanium(IV)

Table 1
Optimisation of $TMSCCl_3$ addition to **1a**[a]



1a **2a**

Run	Promoter	Temp (°C)	Time (h)	**2a**[a] (%)
1	None	rt	1–16	<5
2	TBAT (1 equiv)	−50	1	>95
3	TBAT (10 mol %)	−50	1	>90
4	TBAT (1 mol %)	rt	1	>90 (89)
5	CsF	rt	1–16	<10

[a] Carried out on 1.0 mmol **1a** (0.25 M); conversions to **2a** determined by ^{1}H NMR spectroscopy; in run 4 the isolated yield of **2a** is in parentheses.

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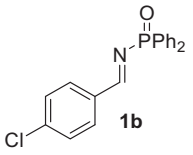
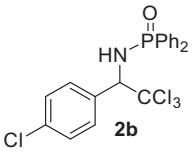
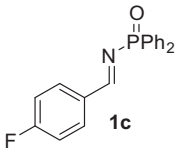
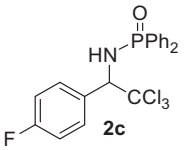
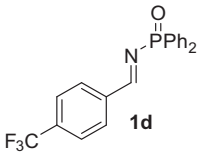
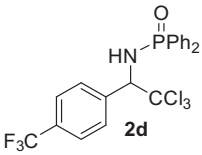
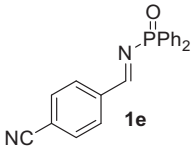
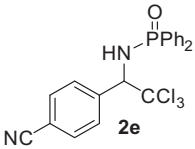
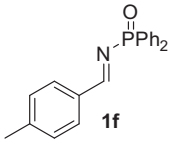
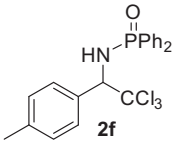
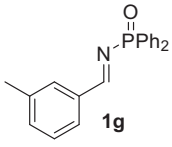
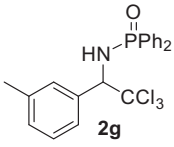
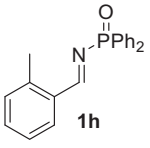
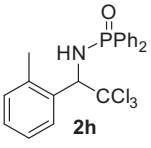
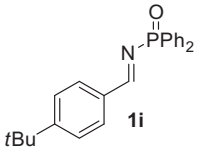
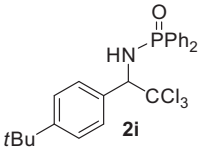
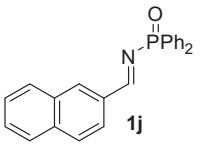
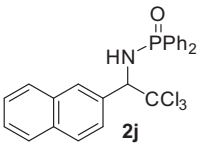
ethoxide promoted condensation between ArCHO and diphenylphosphinic amide in refluxing THF in moderate to very good yields (see Supporting information). Titanium(IV) chloride can also be used as a Lewis acid but it is less convenient to handle (fuming in air) and often leads to lower yields.[14]

The spectroscopic properties of **2a** are in accord with the addition of the trichloromethyl group. In particular, a low-intensity quaternary signal at δ_C 102.7 in the ^{13}C NMR spectrum is assigned to CCl_3 and the molecular ion of **2a** shows the expected Cl_3 isotope pattern. The α-CH group is diagnostically shifted to lower frequencies (δ_H 4.95 in **2a**) compared to its N=CH precursor (δ_H 9.33 in **1a**). A characteristic signal for the amine proton is seen at δ_H 4.07 in the ^1H NMR spectrum, uncorrelated to any ^{13}C NMR signal on HSQC. The conditions of Table 1 (run 4) could be applied to a range of diphenylphosphinoyl benzaldimine substrates, leading to various addition products in 18–95% isolated yields (Table 2).

The reaction is tolerant to electron-withdrawing substituents in *para* positions (runs 1–4: yields from 68% to 94%) and is also effective with electron-donating groups (runs 5–8: yields from 72% to 95%), only showing limitation with a *tert*-butyl group at the *para* position (run 8, 18% yield). Lower yields were associated with isolation issues under chromatography of these polar species rather than underperforming catalysis. However, in many cases, the products could be isolated in analytically pure form by crystallisation. For example, the connectivity of **2c** was confirmed by an X-ray crystallographic study (Fig. 1).

Table 2
Scope of the trichloromethylation reaction[a]

Run	Substrate	Product	Isolated yield (%)
1	 **1b**	 **2b**	84
2	 **1c**	 **2c**	94
3	 **1d**	 **2d**	68
4	 **1e**	 **2e**	72
5	 **1f**	 **2f**	84
6	 **1g**	 **2g**	72
7	 **1h**	 **2h**	95
8	 **1i**	 **2i**	18
9	 **1j**	 **2j**	65

[a] Carried out on 1.0 mmol **1** (0.25 M), 1.5 mmol $TMSCCl_3$, 1 mol % TBAT, room temperature, 1 h. Isolated yields.[15]

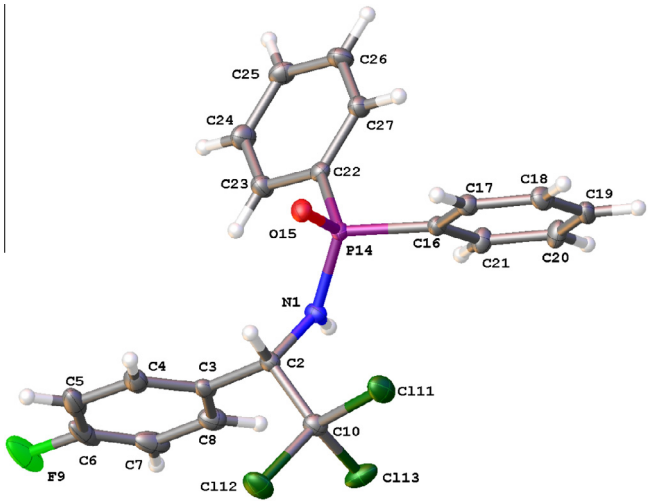
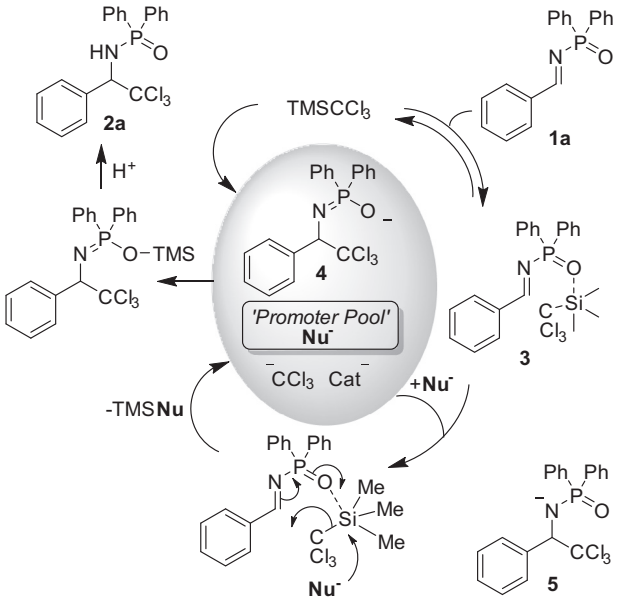


Figure 1. Molecular structure of **2c** (CCDC 1014093). Selected interatomic distances and angles: C(2)–C(10) 1.558, N(1)–C(2) 1.448, N(1)–P(14) 1.649 Å; C(10)–C(2)–N(1) 110.8, P(14)–N(1)–C(2) 124.1, N(1)–P(14)–C(16) 110.1°.



Scheme 1. Proposed catalytic cycle.

One proposed mechanism for the reaction is shown in Scheme 1. Based on our recent mechanistic studies made on 1,4-addition of $TMSCCl_3$ to nitroalkenes,[13] we believe that $TMSCCl_3$ is initially bound to *N*-phosphinoyl benzaldimine **1a** by means of an electron-rich Si–O contact providing **3**. Attack of an external nucleophile, in this case fluoride ions, on **3** triggers CCl_3 transfer presumably through a chair-like transition state, leading to the *N*-phosphinimine anion **4** (1,4-addition mode) or its resonance analogue *N*-phosphinamide **5** (1,2-addition mode). The former (**4**) would itself be an excellent promoter of the reaction able to replace fluoride in further conversion of **3** into **4**. This would explain why only a catalytic amount of TBAT is needed to reach full completion in only one hour (with the concentration of **4** building up over time). *N*-phosphinimine anion **4** can act as a promoter itself or leave the promoter pool by reacting with TMSX (X = CCl_3 or Nu, if Nu is a suitable leaving group) and a final quenching of the reaction leads to *N*-phosphinoyl-α-(trichloromethyl)benzylamine **2**.

In conclusion, the use of $TMSCCl_3$ as a trichloromethylating reagent has great potential in nucleophilic additions to electron-deficient imines. We have achieved, here, the unprecedented catalytic nucleophilic reaction of $TMSCCl_3$ with *N*-phosphinoyl benzaldimines for the synthesis of racemic *N*-phosphinoyl-α-(trichloromethyl)lbenzylamines **2**. Potential development of enantioselective processes will offer significant challenge since the kinetic *N*-phosphinimine anionic product **4** of the reaction is acting itself as a highly effective catalyst of the reaction, and finding a competitive chiral catalyst will be crucial for success.

Acknowledgment

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Supplementary data

Supplementary data (full experimental and spectroscopic data for the compounds **1i** and **2**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.08.122.

References and notes

1. (a) Singer, M. S. *US Patent* 3,796,561, 1974; *Chem. Abstr.* **1974**, *81*, 10486; (b) Cox, J. M.; Clough, J. M.; Barnes, N. J.; Pearson, D. P. J.; Matthews, I. R.; Vohra, S. K.; Smith, S. C.; Mitchell, G.; Barber, R. A. *PCT Int. Appl.* WO 9,533,719, 1995; *Chem. Abstr.* **1996**, *124*, 261022.
2. (a) Hirwe, A. S.; Metcalf, R. L.; Kapoor, I. P. *J. Agric. Food Chem.* **1972**, *20*, 818–824; (b) Weissmueller, J.; Naumann, K.; Stendel, W. *DE Patent* 3,828,543 A1 1990; *Chem. Abstr.* **1990**, *113*, 131715.
3. Brown, D.; Woodcock, D. *Pestic. Sci.* **1975**, *6*, 347–362.
4. (a) Bringmann, G.; God, R.; Feineis, D.; Wesemann, W.; Riederer, P.; Rausch, W. D.; Reichmann, H.; Sontag, K. H. *J. Neural Transm. Suppl.* **1995**, *46*, 245–254; (b) Riederer, P.; Foley, P.; Bringmann, G.; Feineis, D.; Bruckner, R.; Manfred, G. *Eur. J. Pharmacol.* **2002**, *442*, 1–16.
5. Abbaspour Tehrani, K.; Stas, S.; Lucas, B.; De Kimpe, N. *Tetrahedron* **2009**, *65*, 1957–1966.
6. Lee, L. F.; Dolson, M. G.; Howe, R. K.; Stults, B. R. *J. Org. Chem.* **1985**, *50*, 3216–3218.
7. Takamatsu, M.; Sekiya, M. *Chem. Pharm. Bull.* **1980**, *28*, 3098–3105.
8. Shinkevich, E. Y.; Novikov, M. S.; Khlebnikov, A. F. *Synthesis* **2007**, 225–230.
9. Deshmuk, A. R. A. S.; Panse, D. G.; Bhawal, B. M. *Synth. Commun.* **1999**, *29*, 1801–1809.
10. (a) Lukasiewicz, A. *Tetrahedron* **1965**, *21*, 193–202; (b) Wichert-Tur, Z. *Pol. J. Chem.* **1997**, *71*, 739–746.
11. (a) Makosza, M.; Nizamov, S.; Kwast, A. *Mendeleev Commun.* **1996**, *6*, 43–44; (b) Makosza, M.; Ostrowski, S. *Pol. J. Chem.* **2000**, *74*, 1355–1361; (c) Li, Y.; Zheng, T.; Wang, W.; Xu, W.; Ma, Y.; Zhang, S.; Wang, H.; Sun, Z. *Adv. Synth. Catal.* **2012**, *354*, 308–312.
12. (a) Dilman, A. D.; Arkhipov, D. E.; Levin, V. V.; Belyakov, P. A.; Korlyukov, A. A.; Struchkova, M. I.; Tartakovsky, V. A. *J. Org. Chem.* **2007**, *72*, 8604–8607; (b) Fustero, S.; Herrera, L.; Lazaro, R.; Rodriguez, E.; Maestro, M. A.; Mateu, N.; Barrio, P. *Chem. Eur. J.* **2013**, *19*, 11776–11785; (c) Li, Y.; Cao, Y.; Gu, J.; Wang, W.; Wang, H.; Zheng, T.; Sun, Z. *Eur. J. Org. Chem.* **2011**, 676–679.
13. Wu, N.; Wahl, B.; Woodward, S.; Lewis, W. *Chem. Eur. J.* **2014**, *20*, 7718–7724.
14. (a) Jennings, W. B.; Lovely, C. J. *Tetrahedron* **1991**, *47*, 5561–5568; (b) Crampton, R. H.; El Hajjaji, S.; Fox, M. E.; Woodward, S. *Tetrahedron: Asymmetry* **2009**, *20*, 2497–2503.
15. *General procedure for the 1,2-addition reaction of $TMSCCl_3$ with N-phosphinoyl benzaldimines:* TBAT (1 mol %, 5.4 mg) in THF (1 mL) was added to a mixture of imine **1** (1 equiv, 1 mmol) and $TMSCCl_3$ (1.5 equiv, 1.5 mmol) in THF (3 mL) at room temperature. The mixture was stirred for 1 h. After the reaction was complete, a saturated solution of NH_4Cl (1 mL) was added and the quenched reaction mixture was extracted with EtOAc (3×). The combined organic layers were dried over anhydrous $MgSO_4$. Evaporation of the solvent afforded the crude product which was purified by flash chromatography (95:5 CH_2Cl_2/MeOH) to give the corresponding *N*-phosphinoyl-α-(trichloromethyl)benzylamine. Full details of all transformations and associated spectroscopic data are given in Supporting information. *N*-Phosphinoyl benzaldimines **1a–d**, **1f–h** (Ref. 16) and **1e** (Ref. 17) showed identical spectroscopic properties to previously reported samples. Compound **1i**, previously unreported, was fully characterised (see Supporting information).
16. El Hajjaji, S. Ph.D. Thesis, University of Nottingham, 2010.
17. Huang, M.-T.; Wu, H.-Y.; Chein, R.-J. *Chem. Commun.* **2014**, 1101–1103.