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A Novel Reaction of Cyanogen Iodide with Cyclic Tertiary Amines

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Abstract: It has been shown that cyanogen iodide reacts with the tertiary amine ring of marcfortine A (**1**) to give cyano (**4**) and iodocyano (**3**) substituted products. We have now extended this reaction to various cyclic tertiary amines.
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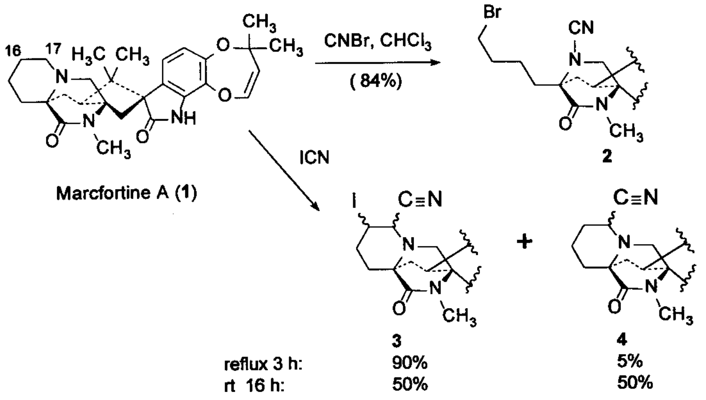
Cyanogen iodide (ICN) has been used extensively in the literature for cyanation of alkenes and aromatic compounds,[1] iodination of aromatic compounds,[2] formation of disulfide bonds in peptides,[3] conversion of dithioacetals to cyanothioacetals,[4] formation of *trans*-olefins from dialkylvinylboranes,[5] lactonization of alkene esters,[6] formation of guanadines,[7] lactimization,[8] formation of α-thioether nitriles,[9] iodocyanation of alkenes,[10] conversion of alkynes to alkyl-iodo alkenes,[11] cyanation/iodination of β-diketones,[12] and formation of alkynyl iodides.[13] During our modification studies on marcfortine A, a fungal metabolite of *Penicillium roqueforti*,[14] we found that treatment with cyanogen bromide gave the ring opened product typical of the von Braun reaction[15] (Scheme 1). However, cyanogen iodide in refluxing chloroform gave entirely different products: *trans*-16-iodo-17-cyanomarcfortine (**3**) and 17-cyanomarcfortine (**4**) in 90% and 5% yields respectively.[16] Lower reaction temperatures seem to favor formation of the cyano product at the expense of the iodocyano product. To the best of our knowledge, this is the first time ICN has been used in this manner.

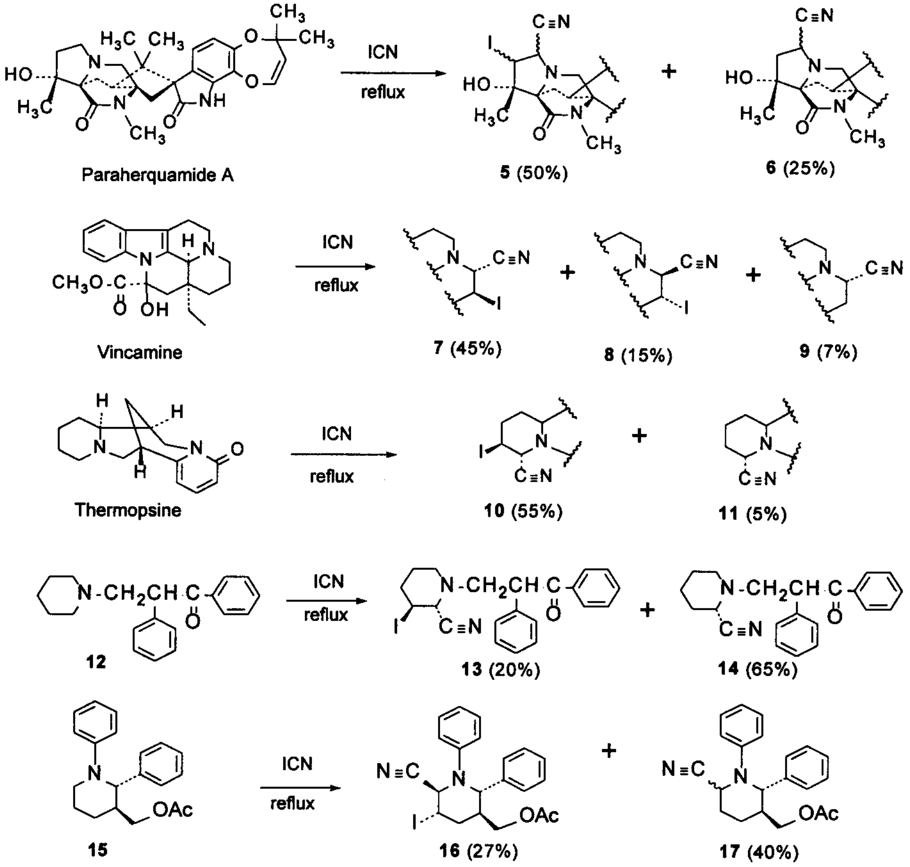
Scheme 1



To demonstrate the generality of the above methodology, we have examined the reaction with different cyclic tertiary amine systems. A number of readily available compounds were subjected to 2-4 equivalents of ICN in chloroform (refluxing or at room temperature).[17]

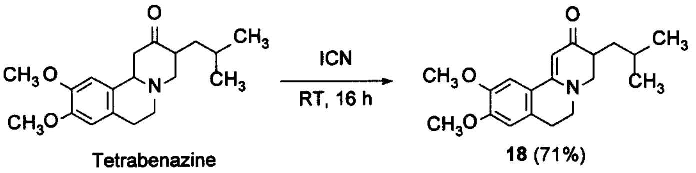
Subjecting complex substrates (Scheme 2) such as vincamine, paraherquamide A, and thermopsine or moderately substituted piperidine derivatives to the above conditions gave the desired *trans*-iodocyano and cyano products. Common functionalities such as hydroxyl, carboxyl, carbonyl, alkoxyl and carboxamido were unaffected by the reaction conditions. Additionally, ring size seemed to be unimportant and chiral centers were not affected.

Scheme 2



This reaction may involve imminium ion and enamine intermediates.[16] An equilibrum between two such intermediates could account for the product ratios. In one case where the putative enamine intermediate was stabilized by conjugation, we were able to isolate it, which supports this mechanism.

Indeed, tetrabenazine when treated with ICN at room temperature gave enamine **18** which was isolated in 71% yield.



In summary, the versatility of cyanogen iodide has been extended to include iodocyanation and cyanation of cyclic tertiary amines in moderate to good yields. Considering the simplicity of the reaction conditions and the generation of products in the absence of an alkene, this method is a convenient way of functionalizing cyclic tertiary amines.

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17. General procedure: Cyanogen iodide (2-4 equiv) was added to a 0.1 M solution of substrate (1 equiv) in $CHCl_3$. The reaction solution was refluxed (or stirred at room temperature) until all of the starting material was consumed as determined by TLC. Saturated sodium sulfite and CH_2Cl_2 were added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 X) and the combined organic layers were washed with saturated sodium sulfite (1 X), 10% aqueous K_2CO_3 (1 X), dried ($MgSO_4$) and concentrated *in vacuo*. The crude mixture was then purified by flash chromatography, PTLC, or chromatotron using EtOAC/Hexanes, Acetone/CH_2Cl_2 or Acetone/Hexanes as the solvent system depending on the substrate and the amount used.

Compound **7**; ^1H NMR (400 MHz, $CDCl_3$) δ 7.6-7.5 (m, 1H), 7.3-7.1 (m, 3H), 4.61 (s, 1H), 4.5-4.4 (m, 1H), 4.2-4.1 (m, 2H), 3.84 (s, 3H), 3.7-3.4 (m, 3H), 3.0-2.2 (m, 6H), 1.5-1.4 (m, 1H), 0.96 (t, *J* = 7.6 Hz). HRMS (FAB): *m/e* 505.0875 ($C_{22}H_{24}I_1N_3O_3$ + H requires 505.0864).

Compound **8**; ^1H NMR (400 MHz, $CDCl_3$) δ 7.6- 7.5 (m, 1H), 7.3-7.1 (m, 3H), 4.66 (s, 1H), 4.4-4.3 (m, 1H), 4.14 (br s, 1H), 3.92 (dd, *J* = 5.5, 14.6 Hz, 1H), 3.85 (s, 3H), 3.73 (d, *J* = 10.9 Hz, 1 H), 3.4-3.3 (m, 1H), 3.1-3.0 (m, 1H), 2.8-2.6 (m, 1H), 2.5-2.1 (m, 5H), 1.5-1.4 (m, 1H), 0.96 (t, *J* = 7.6 Hz). HRMS (FAB): *m/e* 505.0875 ($C_{22}H_{24}I_1N_3O_3$ + H requires 505.0864).

Compound **9**; ^1H NMR (400 MHz, $CDCl_3$) δ 7.6-7.5 (m, 1H), 7.3-7.1 (m, 3H), 4.63 (s, 1H), 4.03 (s, 1H), 3.9-3.8 (m, 1H), 3.84 (s, 3H), 3.6-3.5 (m, 1H), 3.3-3.2 (m, 1H), 3.1-2.9 (m, 1H), 2.7-2.6 (m, 1H), 2.3-1.4 (m, 8H), 0.93 (t, *J* = 7.6 Hz). HRMS (EI): *m/e* 379.1899 ($C_{22}H_{25}N_3O_3$ requires 379.1896).

Compound **18**; ^1H NMR (400 MHz, $CDCl_3$) δ 7.27 (s, 1H), 6.66 (s, 1H), 5.64 (s, 1H), 3.92 (s, 3H), 3.88 (s, 3H), 3.65 (dd, *J* = 5.3, 12.5 Hz, 1H), 3.40 (dd, *J* = 5.5, 12.7 Hz, 2H), 3.31 (dd, *J* = 8.6, 12.6 Hz, 1H), 2.95 (dd, *J* = 6.2, 12.6 Hz, 2H), 2.45 (m, 1H), 1.79-1.69 (m, 2H), 1.34-1.27 (ddd, *J* = 4.8, 13.0, 13.6 Hz, 1H), 0.97 (d, *J* = 6.2 Hz, 3H), 0.92 (d, *J* = 6.3 Hz, 3H). HRMS (FAB): *m/e* 315.1834 ($C_{19}H_{25}NO_3$ + H requires 315.1834).

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