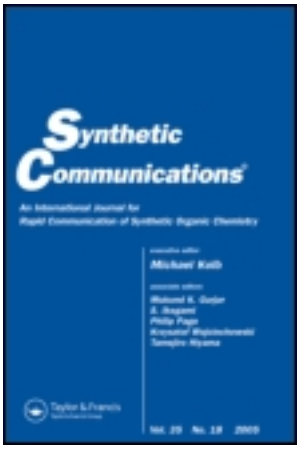

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N-Cyanoimides via the Cyanation of Imides

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N-CYANOIMIDES VIA THE CYANATION OF IMIDES

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ABSTRACT: The conversion of cyclic imides to the corresponding N-cyanoimides has been carried out using cyanogen bromide as the nitrile source. This methodology provides a convenient route for the preparation of both aromatic and aliphatic N-cyanoimides.

Imides are a well known and studied class of compounds possessing a range of interesting properties.[1] N-cyanoimides, on the other hand, are a little known and inadequately studied class of imide derivatives. Although initially reported over a century ago, only a few examples of these compounds can be found in the chemical literature. The earliest examples include the synthesis of N-cyanoacetimide by treating the silver salt of N-cyanoacetamide with acetyl chloride[2a] and the synthesis of N-cyanosuccinimide from cyanamide and succinyl chloride.[2b] More recently, it has been shown that treatment of

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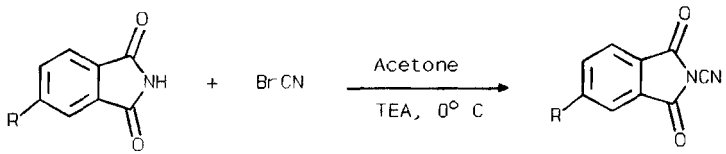
potassium phthalimide with tetracyanomethane provides N-cyanophthalimide.[3] While this method has been applied to other imide salts, the cyanation reagent, tetracyanomethane, is not commercially available and therefore inhibits the use of this methodology.

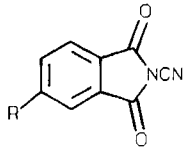
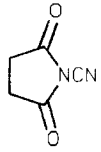
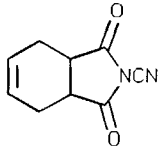
Our research required a convenient, versatile and high yield method for the preparation of various mono and polyfunctional N-cyanoimides. The ready availability of the unsubstituted imide precursors suggested their use as a substrate. Unlike tetracyanomethane, cyanogen halides are also readily available, and have been used previously for the cyanation of phenols,[4] and amines.[5] Being a solid, cyanogen bromide is a more convenient laboratory reagent than cyanogen chloride, a gas. A procedure, reported here, for the cyanation of imides with cyanogen bromide was therefore developed.

Using phthalimide (**1**) as a model substrate, cyanation reactions were carried out with cyanogen bromide in a number of different solvents and in the presence of a variety of bases. While it was possible to prepare N-cyanophthalimide (**2**) under a number of these conditions, acetone was found to be the solvent of choice and triethylamine the most suitable base. If one follows the course of this reaction by GC, the rapid and complete conversion of phthalimide to N-cyanophthalimide at 0 °C is observed. Due to the exothermic nature of this reaction, all reactions were run at 0 °C using an ice bath for external cooling.



1 R = H **2** R = H

Table 1

	Entry	Yield	MP
2	R = H 	77%	189-191 °C
3	R = NO_2	60%	210-211 °C
4	R = CH_3	71%	155-158 °C
5		59%	137-140 °C
6		65%	136-138 °C

† Yield of product obtained by simple recrystallization. Additional product can be obtained from the mother liquor by subsequent recrystallizations.

This methodology can be used to prepare a number of N-cyanoimides as shown in Table 1. The yields given in Table 1 represent the amount of product obtained by simple recrystallization. Additional material could be isolated from the mother liquor by subsequent recrystallizations. The compounds prepared in this study were found to be stable crystalline materials although sensitivity to moisture and strong bases was noted.

The range of substrates in Table 1 demonstrates the clear utility of this synthetic procedure in preparing a variety of aromatic N-cyanoimides as well as aliphatic N-cyanoimides in high yield and purity. This same methodology has also been applied to the preparation of difunctional N-cyanoimides whose utility will be reported elsewhere.

Experimental Section

General. Unless otherwise noted, all solvents and reagents were obtained from commercial suppliers and used without further purification. Triethylamine was distilled from calcium hydride prior to use. Melting points were determined in open capillaries using a Thomas Hoover capillary melting point apparatus and are uncorrected. All new compounds gave satisfactory spectroscopic data. **Caution!** Cyanogen bromide is extremely toxic and due care should be observed at all times. Traces of unreacted cyanogen bromide were destroyed by rinsing laboratory glassware with bleach.[6]

1,3-Dihydro-1,3-dioxo-2*H*-isoindole-2-carbonitrile (N-Cyanophthalimide) (2). To a 25 mL round-bottomed flask was added phthalimide (1.47 g, 10.0 mmol), cyanogen bromide (1.27 g, 12.0 mmol), and 10 mL of acetone. The suspension was stirred and cooled using an ice/salt bath while triethylamine (1.8 mL, 12.8 mmol) was added dropwise over a 2 minute period. After 15 minutes the resulting slurry was transferred to a separatory funnel and partitioned between ethyl acetate and water. The organic phase was washed with water, saturated brine, dried ($MgSO_4$), and filtered. The solution was decolorized with activated charcoal, and concentrated to give a brown solid. This material was recrystallized from ethyl acetate to give 1.32 g (77%) of a

light brown crystalline solid, mp 189-191 °C (Lit.[3] mp 190 °C): IR (nujol) 2258 (nitrile), 1755 (carbonyl) cm^{-1}; ^1H NMR (200 MHz, DMSO) δ 8.05-8.15 (m, 4); ^{13}C NMR (50 MHz, DMSO) δ 162.61, 136.35, 130.76, 125.03, 102.86.

1,3-Dihydro-5-nitro-1,3-dioxo-2*H*-isoindole-2-carbonitrile (3). A 25 mL round-bottomed flask was charged with 4-nitrophthalimide (0.96 g, 5.0 mmol), cyanogen bromide (0.64 g, 6.0 mmol), and 10 mL of acetone. The suspension was stirred and cooled using an ice/salt bath, and triethylamine (1.0 mL, 7.1 mmol) was added dropwise over a 4 minute period. The mixture was allowed to stir for 20 minutes before being partitioned between ethyl acetate and water. The organic phase was washed with water, saturated brine, dried ($MgSO_4$), and concentrated to give 0.95 g of a yellow solid. This material was recrystallized from ethyl acetate to afford 0.65 g (60%) of yellow crystals, mp 210-211 °C (Lit.[3] mp 215 °C): IR (nujol) 2261 (nitrile), 1811 (carbonyl), 1769 (carbonyl), 1533 (nitro), 1343 (nitro) cm^{-1}; ^1H NMR (200 MHz, DMSO) δ 8.34 (d, 1, J = 8.9 Hz), 8.70-8.78 (m, 2); ^{13}C NMR (50 MHz, DMSO) δ 161.15, 160.92, 152.34, 135.19, 132.10, 131.16, 126.48, 119.76, 102.26; GC/MS *m/e* (relative intensity) 217 (77.8), 149 (71.7), 103 (64.4), 75 (100), 74 (52.7).

1,3-Dihydro-1,3-dioxo-5-methyl-2*H*-isoindole-2-carbonitrile (4). To a 250 mL round-bottomed flask was added 4-methylphthalimide[7] (10.00 g, 62.0 mmol), cyanogen bromide (7.00 g, 66.00 mmol), and 75 mL of acetone. The suspension was stirred and cooled using an ice/salt bath. Triethylamine (10.0 mL, 71.7 mmol) was added via syringe over a 15 minute period. The resulting red slurry was allowed to stir for 10 minutes, the cooling bath was removed, and the mixture was allowed to warm to room temperature over about 10 minutes. The solution was filtered to remove the precipitated triethylamine

hydrobromide. The solids were washed with ethyl acetate and the combined filtrates were concentrated using a rotary evaporator. The crude product was transferred to a separatory funnel and partitioned between 2 N hydrochloric acid and a 2:1 mixture of ethyl acetate/hexanes. The organic phase was washed with saturated brine, and dried ($MgSO_4$). The solution was filtered through a short bed of silica gel, then concentrated using a rotary evaporator to give a yellow solid. This material was purified by recrystallization from a mixture of ethyl acetate and toluene to yield 8.22 g (71%) of light brownish yellow crystals, mp 155-158 °C: IR (KBr) 2256 (nitrile), 1792, 1761, 1742, 1610 cm^{-1}; ^1H NMR (200 MHz, DMSO) δ 2.51 (s, 3), 7.75-8.00 (m, 3); ^{13}C NMR (50 MHz, DMSO) δ 162.60, 162.38, 147.99, 136.83, 130.99, 127.99, 125.31, 124.94, 102.84, 43.22; GC/MS *m/e* (relative intensity) 186 (82.9), 142 (9.1), 119 (8.9), 118 (100), 90 (38.3), 89 (45.2), 63 (33.5), 62 (13.6).

N-Cyanosuccinimide (5). To a 250 mL round-bottomed flask was added succinimide (9.91 g, 100 mmol), cyanogen bromide (11.70 g, 110 mmol), and 100 mL of acetone. The suspension was stirred and cooled using an ice/salt bath while triethylamine (16.0 mL, 115 mmol) was added via syringe over a 15 minute period. The ice bath was removed and stirring was continued for 30 minutes. The slurry was diluted with 100 mL of ethyl acetate and filtered to remove the triethylamine hydrobromide. The filter cake was rinsed with additional ethyl acetate. The combined filtrates were concentrated using a rotary evaporator to yield a dark pasty solid. The crude product was transferred to a separatory funnel and partitioned between 2 N hydrochloric acid and ethyl acetate. The organic phase was washed with water, saturated brine, dried ($MgSO_4$), and concentrated to a dark solid using a rotary evaporator. The crude product was recrystallized from ethyl

acetate/hexanes to yield 7.32 g (59%) of fine cinnamon colored flakes, mp 137-140 °C (Lit.[3] mp 138 °C): IR (KBr) 2264 (nitrile), 1759 (carbonyl), 1345, 1111 cm^{-1}; ^1H NMR (200 MHZ, DMSO) δ 2.90 (s, 4); ^{13}C NMR (50 MHz, DMSO) δ 172.98, 102.75, 29.40; GC/MS *m/e* (relative intensity) 124 (100), 96 (20.8), 82 (23.1), 69 (24.1), 56 (48.9), 55 (84.6).

N-Cyano-*cis*-4-cyclohexene-1,2-dicarboximide (6). To a 250 mL round-bottomed flask was added *cis*-4-cyclohexene-1,2-dicarboximide (15.1 g, 100 mmol), cyanogen bromide (11.7 g, 110 mmol), and 100 mL of acetone. The suspension was stirred and cooled with an ice/salt bath. Triethylamine (16.0 mL, 115 mmol) was added via syringe over a 12 minute period. The resulting peach slurry was allowed to stir for 15 minutes. The mixture was diluted with ethyl acetate and filtered to remove solid triethylamine hydrobromide. The filter cake was rinsed with ethyl acetate and the filtrate was concentrated using a rotary evaporator. The crude paste was partitioned between water and a 2:1 mixture of ethyl acetate/hexanes. The organic phase was washed with saturated brine, dried ($MgSO_4$), and concentrated to give a light brown solid. The crude product was purified by recrystallization using ethyl acetate/hexanes to afford 11.5 g (65%) of a glossy off white solid, mp 136-138 °C: IR (nujol) 2256 (nitrile), 1749 (carbonyl) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.30 (ddd, 2, J = 15, 4.4, 2.75 Hz), 2.64 (ddd, 2, J = 15, 3.8, 2.75 Hz), 3.35 (dd, 2, J = 3.5, 2.75 Hz), 5.98 (ddd, 2, J = 3.9, 1.7, 1.5 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.48, 127.52, 100.72, 40.08, 23.26; GC/MS *m/e* (relative intensity) 176 (29.5), 147 (11.1), 107 (20.0), 105 (23.3), 80 (44.0), 79 (100), 78 (35.1).

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