Addition of Alkyl and Aryl Isocyanides to Benzyne

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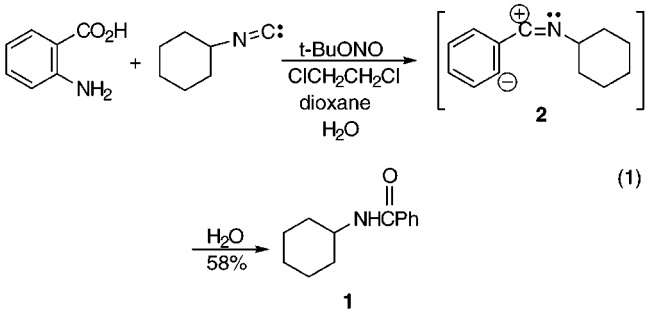
Isocyanates are known to react with a wide range of nucleophilic partners to effect a net installation of a carbamoyl moiety.[1] In contrast to the electrophilic nature of the isocyanate function, the well-known nucleophilicity of isocyanides suggests that this group could serve as an umpoled version of the former species when reacted under certain circumstances with appropriate electrophiles (Figure 1).

We have previously reported that alkyl isocyanides can combine with vinyl isocyanates to afford highly functionalized hydroindolone products[2] and that vinyl isocyanates can also participate in a [4 + 2] cycloaddition with benzyne to provide phenanthridone adducts.[3] We now disclose the results of a study in which alkyl and aryl isocyanides have been found to react with benzynes with reasonable efficiency.[4]



(1)

Treatment of anthranilic acid with excess cyclohexyl isocyanide[5] in the presence of *tert*-butyl nitrite and water in refluxing 1,2-dichloroethane/dioxane afforded benzamide **1**[6] in a serviceable 58% yield (eq 1). The transformation presumably proceeds via addition of the nucleophilic isocyanide to the electrophilic benzyne to afford a zwitterionic intermediate **2** that is rapidly protonated by the water present in the reaction mixture. The resultant *N*-alkylnitrilium ion is then trapped with additional water to provide the observed amide product.[7] Alternatively, the nitrilium ion can be intercepted with isoamyl alcohol to afford the corresponding N-substituted imidate

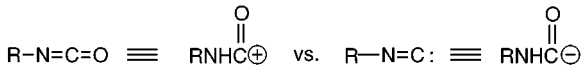
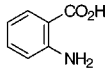
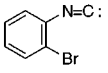
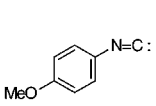
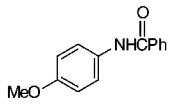
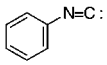
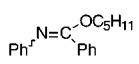
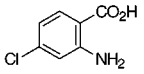
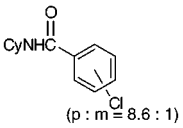
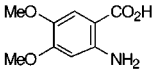
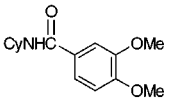
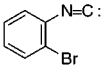
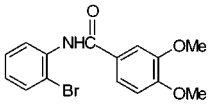


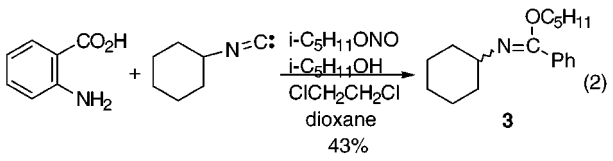
Figure 1. Reactivity relationships between isocyanates and isocyanides.

Table 1. Addition of Isocyanides to Benzyne

Entry	Anthranilic Acid	Isocyanide	Product	Yield (%)
1				46[a]
2	"			48[a]
3	"			35[b]
4		Cy—N=C:	 (p : m = 8.6 : 1)	51[a]
5		"		61[a]
6	"			36[a]

[a] Trapping with H_2O. [b] Trapping with isoamyl alcohol.

ester, which was obtained as a single isomer of undetermined geometry (eq 2).



(2)

Several other examples of these addition reactions that reveal some of the characteristics of the process are compiled in Table 1. The reaction can easily be extended to employ aryl isocyanides as the nucleophile without compromising chemical efficiency. The addition described in entry 3 once again produces a single geometric isomer of undetermined structure, paralleling the observation depicted in eq 2. A particularly noteworthy result is presented in entry 4, in which an 8.6:1 ratio of para-addition to meta-addition products were obtained. Normally, 4-substituted benzynes exhibit little regioselectivity in their additions with reactive nucleophiles; however, less reactive addends can frequently exhibit substantial para/meta ratios due, presumably, to the involvement of a transition state in which substantial charge has already been transferred to the arene ring. Consequently, these reactions can be more sensitive to substituent effects than is typical of this series,[8] and thus,

(1) Richter, R.; Ulrich, H. In *The Chemistry of Cyanates and Their Thio Derivatives*; Patai, S., Ed.; Wiley: Chichester, 1977; Part 2, pp 619−792.
(2) Rigby, J. H.; Qabar, M. *J. Am. Chem. Soc.* **1991**, *113*, 8975.
(3) Rigby, J. H.; Holsworth, D. D.; James, K. *J. Org. Chem.* **1989**, *54*, 4019.
(4) One low-yielding example of this reaction has been reported previously: Knorr, R. *Chem. Ber.* **1965**, *98*, 4014.
(5) Ugi, I.; Meyr, R.; Lipinski, M.; Bodesheim, F.; Rosendahl, F. *Org. Synth.* **1973**, *5*, 300.
(6) Choudary, B. M.; Prasad, A. D.; Bhuma, V.; Swapna, V. *J. Org. Chem.* **1992**, *57*, 5841.
(7) Fry, J. L.; Ott, R. A. *J. Org. Chem.* **1981**, *46*, 3333.
(8) Bunnett, J. F.; Kim, J. K. *J. Am. Chem. Soc.* **1973**, *95*, 2254.

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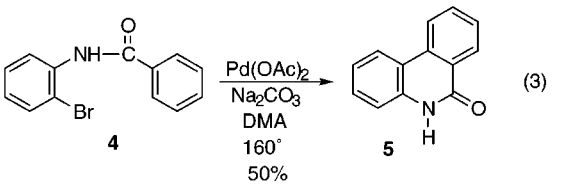
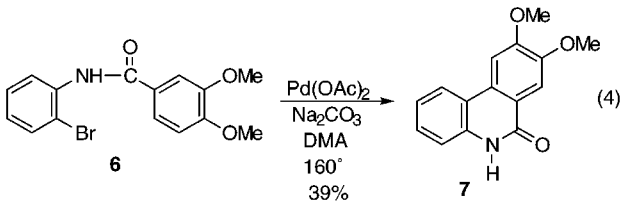
the selectivity seen in entry 4 may be reflective of the relatively mild nucleophilicity of the isocyanide species.





Postaddition manipulations of these adducts are possible when they are appropriately functionalized. For example, the addition products derived from ortho-functionalized aryl isocyanide nucleophiles (entries 1 and 6) are amenable to cyclization to afford phenanthridone products. Equations 3 and 4 depict a palladium(0)-mediated cyclization process[9] to provide the phenanthridones **5**[10] and **7**[11] in useful yields.

In summary, it has been demonstrated that isocyanides can behave as charge-reversed equivalents to isocyanates in reactions with benzyne electrophiles. Further exploitation of this reactivity pattern with other electrophile partners will be reported in due time.

Experimental Section[12]

General Procedure for the Reaction of Cyclohexyl Isocyanide with Benzynes. To a gently refluxing solution of cyclohexyl isocyanide (873 mg, 8.00 mmol), *tert*-butyl nitrite (124 mg, 1.20 mmol), and H_2O (36 mg, 2.00 mmol) in 1,2-dichloroethane (10 mL) was added a solution of the required anthranilic acid (1.00 mmol) dissolved in dioxane (2 mL) over a period of 1.5 h. When the addition was completed, the reaction mixture was refluxed for 30 min, at which time the solution was cooled to room temperature. Water (20 mL) was then added, and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The organic extract was washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure, and the residue was purified by column chromatography to afford the product.

***N*-Cyclohexylbenzamide.** Anthranilic acid (137 mg) gave *N*-cyclohexylbenzamide (118 mg, 58%) as a white solid after column chromatography (10:1 hexane/ethyl acetate): mp 144−6 °C (lit.[6] mp 144−145 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, J = 7 Hz, 2H), 7.46−7.49 (m, 1H), 7.41 (t, J = 8 Hz, 2H), 5.97 (br s, 1H), 3.96−3.99 (m, 1H), 2.02−2.05 (m, 2H), 1.73−1.77 (m, 2H), 1.19−1.65 (m, 6H).

4-Chloro-*N*-cyclohexylbenzamide. 2-Amino-4-chlorobenzoic acid (171 mg) gave 4-chloro-*N*-cyclohexylbenzamide (121 mg, 51%) as a white solid after column chromatography (10:1 hexanes/ethyl acetate): mp 184−5 °C (benzene) (lit.[13] mp 184 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, J = 8.5 Hz, 2H), 7.38 (d, J = 8.5 Hz, 2H), 5.98 (br s, 1H), 3.93−3.96 (m, 1H), 2.00−2.03 (m, 2H), 1.64−1.76 (m, 3H), 1.37−1.45 (m, 2H), 1.18−1.26 (m, 3H).

3,4-Dimethoxy-*N*-cyclohexylbenzamide. 2-Amino-4,5-dimethoxybenzoic acid (197 mg) gave 3,4-dimethoxy-*N*-cyclohexylbenzamide (161 mg, 61%) as a white solid after column chromatography (4:1 hexane/ethyl acetate): mp = 169 °C (EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (s, 1H), 7.23 (d, J = 8.5 Hz, 1H), 6.83 (d, J = 8.5 Hz, 1H), 5.97 (br d, J = 7 Hz, 1H), 3.92 (s, 4H), 3.90 (s, 3H), 2.00−2.02 (m, 2H), 1.73−1.75 (m, 2H), 1.63−1.66 (m, 1H), 1.37−1.45 (m, 2H), 1.17−1.25 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.2, 151.5, 148.9, 127.7, 119.0, 110.6, 110.1, 56.0, 48.7, 33.3, 25.6, 25.0; IR ($CHCl_3$) ν 2395, 1625 cm^{-1}; MS *m/e* 263 (M^+, 35), 181 (90), 165 (100); mass calcd for $C_{15}H_{21}NO_3$ 263.1521, found 263.1526.

General Procedure for the Reaction of Aryl Isocyanides with Benzynes. To a gently refluxing solution of the required aryl isocyanide (8.00 mmol) and H_2O (36 mg, 2.00 mmol) in 1,2-dichloroethane (10 mL) was added simultaneously a solution of isoamyl nitrite (176 mg, 1.5 mmol) in dioxane and a solution of the desired anthranilic acid (1.00 mmol) in dioxane (2 mL) via two addition funnels over a period of 1.5 h. When the addition was completed, the reaction mixture was refluxed for 30 min, at which time the solution was cooled to room temperature. Water (20 mL) was then added, and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The organic extract was washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure, and the residue was purified by column chromatography to afford the product.

***N*-(2-Bromophenyl)benzamide.** Anthranilic acid (137 mg) and 2-bromophenyl isocyanide (1.45 g) gave *N*-(2-bromophenyl)-benzamide (127 mg, 46%) as a pale yellow solid after column chromatography (20:1 hexanes/ethyl acetate): mp 115 °C (ethanol) (lit.[14] mp 116 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.56 (dd, J = 1.5, 8.5 Hz, 1H), 8.47 (br s, 1H), 7.94 (d, J = 7 Hz, 2H), 7.59 (t, J = 7 Hz, 2H), 7.52 (t, J = 8 Hz, 2H), 7.38 (dd, J = 1, 7.5 Hz, 1H), 7.02 (dd, J = 1, 8.5 Hz, 1H).

***N*-(2-Bromophenyl)-3,4-dimethoxybenzamide.** 2-Amino-4,5-dimethoxybenzoic acid (197 mg) and 2-bromophenyl isocyanide (1.45 g) gave *N*-(2-bromophenyl)-3,4-dimethoxybenzamide (121 mg, 36%) as a yellow solid after column chromatography (4:1 hexanes/ethyl acetate): mp 149−151 °C (ethanol) (lit.[15] mp 148.5−150 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54 (dd, J = 1.5, 8.5 Hz, 1H), 8.43 (br s, 1H), 7.58 (dd, J = 1.5, 8 Hz, 1H), 7.54 (d, J = 1.5 Hz, 1H), 7.48 (dd, J = 2, 8 Hz, 1H), 7.37 (t, J = 8.5 Hz, 1H), 7.01 (dd, J = 1.5, 8 Hz, 1H), 6.95 (d, J = 8.5 Hz, 1H), 3.98 (s, 3H), 3.96 (s, 3H).

***N*-(4-Methoxyphenyl)benzamide.** Anthranilic acid (137 mg) and 4-methoxyphenyl isocyanide (1.06 g) gave *N*-(4-methoxyphenyl)benzamide (109 mg, 48%) as a yellow solid after column chromatography (4:1 hexanes/ethyl acetate): mp 156 °C (benzene) (lit.[16] mp 153 °C from ^{i}Pr$_2$O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, J = 7.5 Hz, 3H), 7.44−7.54 (m, 5H), 6.89 (d, J = 9 Hz, 2H), 3.80 (s, 3H).

General Procedure for the Synthesis of Aryl Isocyanides.[17] The required formanilide (50 mmol) was dissolved in diisopropylamine (13.7 g, 135 mmol) and CH_2Cl_2 (50 mL). The mixture was cooled to 0 °C, and $POCl_3$ (8.4 g, 55 mmol) was added dropwise. Stirring was continued at 0 °C for 1 h, after which time sodium carbonate (10 g) in water (50 mL) was added at a rate so that the temperature was maintained at 25−30 °C. The mixture was stirred for 1 h at room temperature, and then more water (50 mL) and CH_2Cl_2 (25 mL) were added. The organic layer was washed with water (3 × 25 mL), dried over anhydrous $MgSO_4$, and evaporated under reduced pressure to afford the crude product, which was then purified by distillation or recrystallization.

2-Bromophenyl Isocyanide. *N*-(2-Bromophenyl)formamide (10 g) gave 2-bromophenyl isocyanide (4.16 g, 45%) as white needles after recrystallization (hexanes): mp 41 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, J = 8 Hz, 1H), 7.44 (d, J = 8 Hz, 1H), 7.35 (t, J = 8 Hz, 1H), 7.27 (t, J = 8 Hz, 1H); ^{13}C NMR

(9) Ames, D. E.; Opalko, A. *Tetrahedron* **1984**, *40*, 1919.
(10) Yang, N. C.; Shani, A.; Lenz, G. R. *J. Am. Chem. Soc.* **1966**, *88*, 5369.
(11) Narasimhan, N. S.; Chandrachood, P. S. *Tetrahedron* **1981**, *37*, 825.
(12) For general experimental details, see: Rigby, J. H.; Qabar, M.; Ahmed, G.; Hughes, R. C. *Tetrahedron* **1993**, *49*, 10219.
(13) Ono, M.; Araya, I.; Todoriki, R.; Tamura, S. *Chem. Pharm. Bull.* **1990**, *38*, 1824.
(14) Bunnett, J. F. Hrutfiord, B. F. *J. Am. Chem. Soc.* **1961**, *83*, 1691.
(15) Kasum, B.; Prager, R. H. *Aust. J. Chem.* **1983**, *36*, 1455.
(16) Pocar, D.; Roversi, E.; Trimarco, P.; Valgattarri, G. *Justus Liebigs Ann. Chem.* **1995**, 487.
(17) Obrecht, R.; Herrmann, R.; Ugi, I. *Synthesis* **1985**, 400.

(125 MHz, $CDCl_3$) δ 168.4, 133.3, 130.4, 128.2, 128.1, 119.9; IR (CH_2Cl_2) ν 2138 cm^{-1}.

4-Methoxyphenyl Isocyanide. *N*-(4-Methoxyphenyl)formamide (7.55 g) gave 4-methoxyphenyl isocyanide (4.10 g, 62%) as a pale yellow oil after distillation: bp 76 °C/1 mmHg. Analytical data were identical to those reported in the literature.[18]

Phenyl Isocyanide. Formanilide (6.05 g) gave phenyl isocyanide (2.60 g, 50%) as a yellow oil after distillation: bp 62 °C/16 mmHg (lit.[19] bp 50−51 °C/11 mmHg).

General Procedure for the Synthesis of Imidate Esters. To a gently refluxing solution of the required isocyanide (8.00 mmol), isoamyl nitrite (141 mg, 1.20 mmol), and isoamyl alcohol (264 mg, 3.00 mmol) in 1,2-dichloroethane (10 mL) was added a solution of anthranilic acid (137 mg, 1.00 mmol) in dioxane (2 mL) over a period of 1.5 h. When the addition was completed, the reaction mixture was refluxed for 30 min, after which time the solution was cooled to room temperature. The solvent was removed under reduced pressure, and the residue was placed under high vacuum (0.1 mmHg) for 45 min at 35 °C to remove the bulk of unreacted isocyanide. The product was obtained by filtration through a plug of silica gel (10:1 hexanes/ethyl acetate/1% Et_3N).

Isopentyl *N*-Cyclohexylbenzimidate. Cyclohexyl isocyanide (873 mg) gave the product (118 mg, 43%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28−7.41 (m, 5H), 4.20 (t, J = 6.6 Hz, 2H), 3.1−3.2 (m, 1H), 1.18−1.80 (m, 13H), 0.95 (d, J = 6.9 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 133.4, 128.9, 128.2, 127.6, 63.6, 57.6, 37.7, 35.0, 25.7, 25.2, 24.5, 22.7; IR (neat) ν 2921, 2844, 1661, 1442, 1259, 1111, 1076 cm^{-1}; MS *m/e* 273 (M^+, 3), 105 (100); mass calcd for $C_{18}H_{27}NO$ 273.2092, found 273.2088.

Isopentyl *N*-Phenylbenzimidate. Phenyl isocyanide (824 mg) gave the product (94 mg, 35%) as a greenish oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14−7.32 (m, 7H), 6.45 (tt, J = 1.2 Hz, J = 7.5 Hz, 1H), 6.72 (dd, J = 1.2, 8.4 Hz, 2H), 4.38 (t, J = 7.2 Hz, 2H), 1.86 (m, 1H), 1.72 (q, J = 7.2 Hz, 2H), 1.00 (d, J = 7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.6, 131.6, 129.7, 129.3, 128.8, 127.8, 122.4, 121.7, 65.2, 37.6, 25.3, 22.6; IR (neat) ν 2950, 1647, 1590, 1259, 1104, 682 cm^{-1}; MS *m/e* 267 (M^+, 3), 105 (100); mass calcd for $C_{18}H_{21}NO$ 267.1623, found 267.1618.

6(5*H*)-Phenanthridinone. *N*-(2-Bromophenyl)benzamide (50 mg, 0.18 mmol), palladium(II) acetate (4 mg, 0.018 mmol), and anhydrous sodium carbonate (23 mg, 0.21 mmol) in *N*,*N*-dimethylacetamide (2 mL) were heated together at 160 °C for 2.5 h. The resultant mixture was cooled to room temperature, poured into water (5 mL), and extracted with EtOAc (3 × 5 mL). The organic extract was dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. Column chromatography of the crude product (4:1 hexanes/ethyl acetate) gave a white solid (18 mg, 50%): mp 289 °C (lit.[10] mp 291−292 °C); ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.67 (br s, 1H), 8.49 (d, J = 8 Hz, 1H), 8.37 (d, J = 8 Hz, 1H), 8.30 (dd, J = 1 Hz, J = 8 Hz, 1H), 7.84 (dt, J = 1, 8.5 Hz, 1H), 7.63 (t, J = 7.5 Hz, 1H), 7.47 (dt, J = 1, 8 Hz, 1H), 7.35 (d, J = 7.5 Hz, 1H), 7.25 (dt, J = 1, 8 Hz, 1H).

8,9-Dimethoxy-5*H*-phenanthridin-6-one. *N*-(2-Bromophenyl)-3,4-dimethoxybenzamide (41 mg, 0.122 mmol), palladium(II) acetate (5.4 mg, 0.024 mmol), and anhydrous sodium carbonate (15 mg, 0.146 mmol) in *N*,*N*-dimethylacetamide (2 mL) were heated at 160 °C for 2.5 h. The mixture was cooled to room temperature, poured into water (5 mL), and extracted with EtOAc (3 × 5 mL). The organic extract was dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. Column chromatography of the crude product (4:1 hexanes/ethyl acetate) gave a pale yellow solid (12 mg, 39%): mp 296 °C (ethanol) (lit.[11] mp 296 °C); ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.58 (br s, 1H), 8.37 (d, J = 8 Hz, 1H), 7.86 (s, 1H), 7.67 (s, 1H), 7.41 (t, J = 7.5 Hz, 1H), 7.31 (d, J = 8 Hz, 1H), 7.22 (t, J = 7.5 Hz, 1H), 4.00 (s, 3H), 3.88 (s, 3H).

Acknowledgment. The authors wish to thank the National Science Foundation for their generous support of this research.

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(18) Casanova, J., Jr.; Werner, N. D.; Schuster, R. E. *J. Org. Chem.* **1966**, *31*, 3473.

(19) Ugi, I.; Fetzer, U.; Eholzer, U.; Knupfer, H.; Offermann, K. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 472.