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ortho-Lithiophenyl Isocyanide: A Versatile Precursor for 3*H*-Quinazolin-4-ones and 3*H*-Quinazolin-4-thiones

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ABSTRACT

***ortho*-Lithiophenyl isocyanide has been generated from *ortho*-bromophenyl isocyanide and successfully employed toward the synthesis of 2-substituted phenyl isocyanides as well as 2,3-disubstituted 3*H*-quinazoline-4-ones and 3*H*-quinazolin-4-thiones.**

Isocyanides have found a wide range of applications in organic synthesis,[1] particularly in the synthesis of heterocycles.[2] The electron-withdrawing effect of the isocyano group enhances the acidity of α-C,H bonds, and this was first exploited by Schöllkopf and Gerhart[3] (Figure 1) in 1968. Since then, α-metallated isocyanides have been shown to participate in various types of cocyclizations leading to different nitrogen-containing heterocycles.[4] Conversely, the synthesis of indoles by the cyclization of *ortho*-methylphenyl isocyanides metallated at the benzylic position has been reported by Ito and Saegusa et al.[5] and later was carried out

Figure 1. Different types of metallated isocyanides.

(1) For reviews, see: (a) Ito, Y. *Science of Synthesis*; Suginome, S.-I.,; Murahashi, M., Eds.; Thieme, Stuttgart, 2004; Vol. 19, pp 445−530. (b) For recent reviews on multicomponent reactions with isocyanides, see:(c) Bienayme, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem.−Eur. J.* **2000**, *6*, 3321–3329. (d) Zhu, J. *Eur. J. Org. Chem.* **2003**, 1133–1144. (e) Nair, V.; Rajesh, C.; Vinod, A. U.; Bindu, S.; Sreekanth, A. R.; Mathen, J. S.; Balagopal, L. *Acc. Chem. Res.* **2003**, *36*, 899–907. (f) Dömling, A. *Chem. Rev.* **2006**, *106*, 17–89. (g) Dömling, A.; Ugi, I. *Angew. Chem.* **2000**, *112*, 3300–3344; *Angew. Chem., Int. Ed.* **2000**, *39*, 3168−3210. (h) For reviews on palladium-catalyzed insertions of isocyanides, see: (i) Heck, R. F. *Palladium Reagents in Organic Synthesis*; Academic Press: New York, 1985. (j) Tsuji, J. *Palladium Reagents and Catalysts*; John Wiley: Chichester, U.K., 1995. (k) Ito, Y.; Suginome, M. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., de Meijere, A., Eds.; Wiley: New York, 2002.

(2) For some recently reported syntheses of heterocycles from isocyanides, see: (a) Fujiwara, S.-i.; Asanuma, Y.; Shin-ike, T.; Kambe, N. *J. Org. Chem.* **2007**, *72*, 8087–8090. (b) Gilley, C. B.; Kobayashi, Y. *J. Org. Chem.* **2008**, *73*, 4198–4204. (c) St. Cyr, D. J.; Martin, N.; Arndtsen, B. A *Org. Lett.* **2007**, *9*, 449–452. (d) Winkler, J. D.; Asselin, S. M. *Org. Lett.* **2006**, *8*, 3975–3977. (e) Kanazawa, C.; Kamijo, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **2006**, *128*, 10662–10663. (f) Kamijo, S.; Kanazawa, C.; Yamamoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 9260–9266. (g) Larionov, O. V.; de Meijere, A. *Angew. Chem.* **2005**, *117*, 5809–5813; *Angew. Chem., Int. Ed.* **2005**, *44*, 5664−5667.

(3) Schöllkopf, U.; Gerhart, F. *Angew. Chem.* **1968**, *80*, 842–843; *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 805−806.

(4) For a review, see: (a) Schöllkopf, U. *Angew. Chem.* **1977**, *89*, 351–360; *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 339−348 and references therein. (b) Schöllkopf, U.; Lau, H.-H.; Scheunemann, K.-H.; Blume, E.; Madawinata, K. *Liebigs Ann. Chem.* **1980**, *4*, 600–610.

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employing transition metal catalysts.[6] We envisaged that ortho-metallated phenyl isocyanides which, to our knowledge, are not known[7] could also be versatile precursors for certain types of heterocycles.

In particular, 3*H*-quinazolin-4-ones, some derivatives of which occur as natural products[8,9] (Figure 2), might be

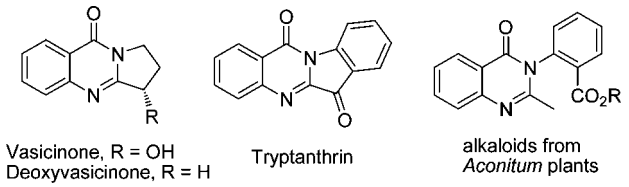
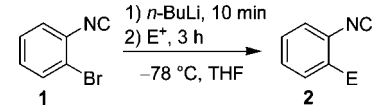


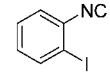
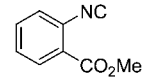
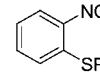
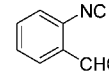
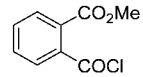
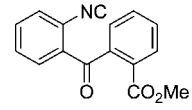
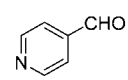
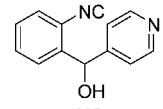
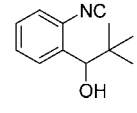
Figure 2. Some naturally occurring 3*H*-quinazolin-4-ones.[8,9]

accessible by reactions of such ortho-metallated phenyl isocyanides with isocyanates. This would be extremely useful, as 3*H*-quinazolin-4-ones have been reported to possess a vast range of biological activities, including analgesic, anti-Parkinsonian, CNS depressant, and CNS stimulating as well as tranquilizing, antidepressant, and anticonvulsant effects. Some of these compounds also act as psychotropic, hypnotic, cardiotonic, and antihistamine agents[10,11] and possess cardiovascular activity as well as antiinflammatory activity.[10,12] Quinazolinones also inhibit monoamine oxidase, aldose reductase, tumor necrosis factor R, thymidylate synthase, pyruvic acid oxidation, as well as acetylcholine-esterase activity and are antitumor, antiulcer, antiplatelet aggregation (glycoprotein IIb/IIIa inhibitors),[13] and hypoglycemic agents.[10,14] They are also potent antibacterial, antifungal, antiviral, antimycobacterial, and antimalarial agents.[10] Therefore, not surprisingly, they have been included in the list of molecules with "privileged structure"[15] for combinatorial chemistry, capable of binding to multiple receptors with high affinity.[16] Many of the numerous reported syntheses of these heterocycles start from anthranilic acid or its derivatives, but none of them use the advantages of isocyanide chemistry.[17,18]

To investigate the possibility of generating ortho-metallated phenyl isocyanide, two possible precursors for halogen−metal exchange reactions, *ortho*-bromo- and *ortho*-iodophenyl isocyanides **1** and **2a**, were synthesized. The iodo derivative **2a** turned out to undergo fast (<10 min) transmetallation reactions, when it was treated with *n*-BuLi, *t*-BuLi (−100 °C), or *i*-PrMgCl·LiCl[19] (−78 °C) in THF. The target *ortho*-lithiophenyl isocyanide could also be obtained from the bromo derivative **1**, synthesized from inexpensive 2-bromoaniline. The best and most reproducible results, in this case, were achieved with *n*-BuLi in THF at −78 °C. Different electrophiles were tested in their reaction with *ortho*-lithiophenyl isocyanide generated in situ in this way (Table 1). The respective 2-substituted phenyl isocyanides (**2**) were obtained in high yields (71−88%), except for 2-formylphenyl isocyanide **2d** (55%). The standard reagent for the electrophilic installation of a formyl group,

Table 1. Synthesis of 2-Substituted Phenyl Isocyanides



electrophile	product of type **2**		yield (%)
I_2		**2a**	88
$ClCO_2Me$		**2b**	79
PhSSPh		**2c**	84
MeOCHO		**2d**	55
		**2e**	79
		**2f**	71
		**2g**	80

(5) (a) Ito, Y.; Kobayashi, K.; Saegusa, T. *J. Am. Chem. Soc.* **1977**, *99*, 3532–3534. (b) Ito, Y.; Kobayashi, K.; Saegusa, T. *J. Org. Chem.* **1979**, *44*, 2030–2032. (c) Ito, Y.; Kobayashi, K.; Seko, N.; Saegusa, T. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 73–84.

(6) (a) Jones, W. D.; Kosar, W. P. *J. Am. Chem. Soc.* **1986**, *108*, 5640–5641. (b) Michelin, R. A.; Facchin, G.; Braga, D.; Sabatino, P. *Organometallics* **1986**, *5*, 2265–2274.

(7) α-Addition of organolithium reagents to phenyl isocyanide followed by its ortho-metallation has been reported: Walborsky, H. M.; Ronman, P. *J. Org. Chem.* **1978**, *43*, 731–734.

(8) (a) Snider, B. B.; Wu, X. *Org. Lett.* **2007**, *9*, 4913–4915. (b) Oh, C. H.; Song, C. H. *Synth. Commun.* **2007**, *37*, 3311–3317. (c) Linder, M. R.; Heckeroth, A. R.; Najdrowski, M.; Daugschies, A.; Schollmeyer, D.; Miculka, C. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4140–4143. (d) Bowman, W. R.; Elsegood, M. R. J.; Stein, T.; Weaver, G. W. *Org. Biomol. Chem.* **2007**, *5*, 103–113. (e) Duvall, J. R.; Wu, F.; Snider, B. B. *J. Org. Chem.* **2006**, *71*, 8579–8590. (f) Shim, S. H.; Kim, J. S.; Son, K. H.; Bae, K. H.; Kang, S. S. *J. Nat. Prod.* **2006**, *69*, 400–402. (g) Jao, C.-W.; Lin, W.-C.; Wu, Y.-T.; Wu, P.-L. *J. Nat. Prod.* **2008**, *71*, 1275–1279.

(9) For recent reviews on quinazoline alkaloids, see: (a) Michael, J. P. *Nat. Prod. Rev.* **2004**, *21*, 650–668. (b) Michael, J. P. *Nat. Prod. Rep.* **2008**, 166–187.

(10) Sinha, S.; Srivastava, M. *Prog. Drug Res.* **1994**, *43*, 143.

(11) Nagase, T.; Mizutani, T.; Ishikawa, S.; Sekino, E.; Sasaki, T.; Fujimura, T.; Ito, S.; Mitobe, Y.; Miyamoto, Y.; Yoshimoto, R.; Tanaka, T.; Ishihara, A.; Takenaga, N.; Tokita, S.; Fukami, T.; Sato, N. *J. Med. Chem.* **2008**, *51*, 4780–4789.

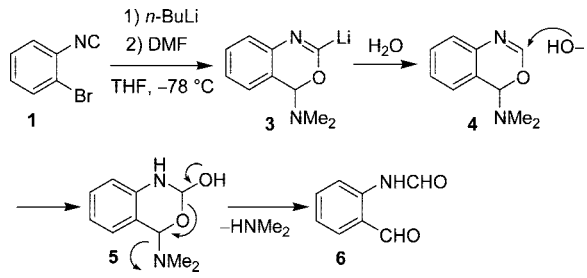
(12) de Laszlo, S. E.; Quagliato, C. S.; Greenlee, W. J.; Patchett, A. A.; Chang, R. S. L.; Lotti, V. J.; Chen, T.-B.; Scheck, S. A.; Faust, K. A.; Kivlighn, S. S.; Schorn, T. S.; Zingaro, G. J.; Siegl, P. K. S. *J. Med. Chem.* **1993**, *36*, 3207–3210.

(13) (a) Liverton, N. J.; Armstrong, D. J.; Claremon, D. A.; Remy, D. C.; Baldwin, J. J.; Lynch, R. J.; Zhang, G.; Gould, R. J. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 483–486. (b) Zhang, W.; Mayer, J. P.; Hall, S. E.; Weigel, J. A. *J. Comb. Chem.* **2001**, *3*, 255–256.

(14) Gopalsamy, A.; Yang, H. *J. Comb. Chem.* **2000**, *2*, 378–381.

dimethyl formamide, in this case led to 2-(formylamino)benzaldehyde **6**, which presumably was formed by base-catalyzed hydrolysis of the initially formed 1,3-benzooxazine derivative **4** under the aqueous workup conditions (Scheme 1).

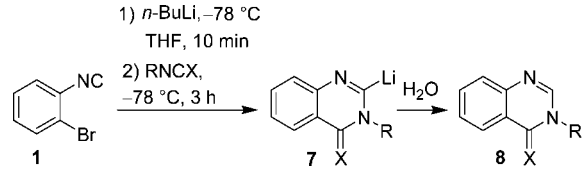
Scheme 1



The 2-substituted phenyl isocyanides prepared in this way can be used for many purposes, particularly in multicomponent Ugi−Passerini reactions[1b] or for the synthesis of correspondingly substituted anilines, to which isocyanides can easily be hydrolyzed under acidic conditions.[20]

When isocyanates and isothiocyanates were employed as electrophiles, cyclic 3*H*-quinazolin-4-ones (-thiones) **8** were formed in high yields (69−91%) (Table 2).

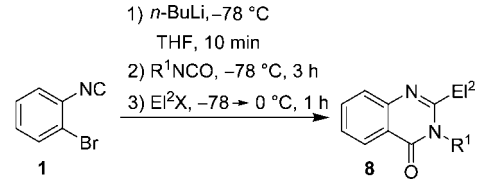
Table 2. Synthesis of 3*H*-Quinazolin-4-ones 3*H*-Quinazolin-4-thiones **8**

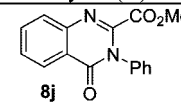
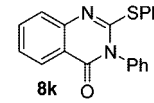
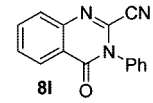
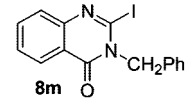
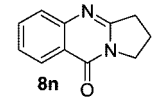
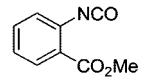
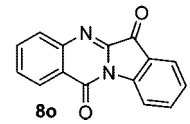


RNCX			
R	X	product	yield (%)
Ph	O	**8a**	91
4-MeC_6H_4	O	**8b**	89
4-$CF_3C_6H_4$	O	**8c**	69
4-FC_6H_4	O	**8d**	75
$PhCH_2$	O	**8e**	74
iPr	O	**8f**	81
cPr	O	**8g**	70
cPr	S	**8h**	71
cHex	S	**8i**	78

Typically, the reactions with isocyanates were carried out at −78 °C and quenched with water at the same temperature, but in the case of isothiocyanates the mixtures were gradually warmed to −40 °C before quenching. In contrast to these reactions of a β-lithiated isocyanide, α-lithiated isocyanides have been reported mainly to give bisadducts with isocyanates,[4a] indicating that the metallated five-membered heterocyclic intermediates formed in that case were much

Table 3. Synthesis of 2,3-Disubstituted 3*H*-Quinazolin-4-ones **8**



isocyanate	electrophile El^2X	product of type **8**, yield (%)	yield (%)
PhNCO	$ClCO_2Me$	 **8j**	73
PhNCO	PhSSPh	 **8k**	77
PhNCO	TosCN	 **8l**	54
$PhCH_2NCO$	I_2	 **8m**	75
$I(CH_2)_3NCO$	—	 **8n**	72
	—	 **8o**	85

(15) Evans, B. E.; Rittle, K. E.; Bock, M. G.; DiPardo, R. M.; Freidinger, R. M.; Whitter, W. L.; Lundell, G. F.; Veber, D. F.; Anderson, P. S.; Chang, R. S. L.; Lotti, V. J.; Cerino, D. J.; Chen, T. B.; Kling, P. J.; Kunkel, K. A.; Springer, J. P.; Hirshfield, J. *J. Med. Chem.* **1988**, *31*, 2235–2246.

(16) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893–930.

(17) For reviews, see: (a) Undheim, K.; Benneche, T. *Comprehensive Heterocyclic Chemistry II*; Pergamon: Oxford, 1998; Vol. 6. (b) Connolly, D. J.; Cusack, D.; O'Sullivan, T. P.; Guiry, P. J. *Tetrahedron* **2005**, *61*, 10153–10202.

(18) For some recently published syntheses of 3*H*-quinazolin-4-ones, see: (a) Zeghida, W.; Debray, J.; Chierici, S.; Dumy, P.; Demeunynck, M. *J. Org. Chem.* **2004**, *73*, 2473–2475. (b) Mhaske, S. B.; Argade, N. P. *J. Org. Chem.* **2004**, *69*, 4563–4566.

(19) (a) Krasovskiy, A.; Knochel, P. *Angew. Chem.* **2004**, *116*, 3396–3399; *Angew. Chem., Int. Ed.* **2004**, *43*, 3333−3336. (b) Ren, H.; Krasovskiy, A.; Knochel, P. *Org. Lett.* **2004**, *6*, 4215–4217.

(20) Schöllkopf, U.; Henneke, K.-W.; Madawinata, K.; Harms, R. *Justus Liebigs Ann. Chem.* **1977**, *1*, 40–50.

(21) (a) Murdoch, R.; Tully, W. R.; Westwood, R. *J. Heterocycl. Chem.* **1986**, *23*, 833–841. (b) Chenard, B. L.; Welch, W. M.; Blake, J. F.; Butler, T. W.; Reinhold, A.; Ewing, F. E.; Menniti, F. S.; Pagnozzi, M. J. *J. Med. Chem.* **2001**, *44*, 1710–1717. (c) Bilokin, Y. V.; Kovalenko, S. M. *Heterocycl. Commun.* **2000**, *6*, 409–414.

(22) (a) Bowman, W. R.; Elsegood, M. R. J.; Stein, T.; Weaver, G. W. *Org. Biomol. Chem.* **2007**, *5*, 103–113. (b) Tangirala, R.; Antony, S.; Agama, K.; Curran, D. P. *Synlett* **2005**, *18*, 2843–2846. (c) Kaneko, C.; Kasai, K.; Katagiri, N.; Chiba, T. *Chem. Pharm. Bull.* **1986**, *34*, 3672–3681.

(23) Perdicaro, A.; Granata, G.; Marrazzo, A.; Santagati, A. *Synth. Commun.* **2008**, *38*, 723–737.

more reactive than the lithiated derivatives of type **7** formed from the β-lithiated isocyanide. This makes it possible to further diversify the 2-substituent of the 3*H*-quinazolin-4-ones (-thiones) **8** by trapping the intermediate **7** with a second electrophile El^2X in the same flask.

Various 2,3-disubstituted 3*H*-quinazolin-4-ones **8j**−**o** could thus be conveniently prepared from 2-bromophenyl isocyanide **1**-Br in a three-step one-pot sequence (Table 3). 2-Halo-3*H*-quinazolin-4-ones of type **8m** have been reported to undergo substitution with nucleophiles[21] and also participate in different radical cyclization processes,[22] which opens access to a large variety of substituted 3*H*-quinazolin-4-ones.

Copper-catalyzed couplings of aryl thioethers of type **8k** with aryl iodides have also been reported.[23] Quenching of the lithiated intermediates of type **7** with electrophiles can also occur intermolecularly, when the initially employed isocyanate already contains an appropriate functional group. Thus, 3-iodopropyl isocyanate and methyl 2-isocyanatobenzoate in one step gave 3*H*-quinazolin-4-ones **8n** and **8o** in 72 and 85% yield, respectively. Both deoxyvasicinone **8n**[24] and tryptanthrine **8o**[25] are naturally occurring alkaloids with important biological activities.

In conclusion, 2-substituted phenyl isocyanides are easily obtained by halogen−lithium exchange of *ortho*-bromophenyl isocyanide and subsequent trapping of the thus generated *ortho*-lithiophenyl isocyanide with electrophiles. This strategy has been effectively employed for the new three-step one-pot synthesis of substituted 3*H*-quinazolin-4-ones (-thiones) including the naturally occurring alkaloids deoxyvasicinone and tryptanthrine.

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Supporting Information Available: Experimental procedures and full characterization for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(24) For selected examples of recent syntheses of deoxyvasicinone, see: (a) Mhaske, S. B.; Argade, N. P. *J. Org. Chem.* **2001**, *66*, 9038–9040. (b) Liu, J.-F.; Ye, P.; Sprague, K.; Sargent, K.; Yohannes, D.; Baldino, C. M.; Wilson, C. J.; Ng, S.-C. *Org. Lett.* **2005**, *7*, 3363–3366. (c) Lee, E. S.; Park, J.-G.; Jahng, Y. *Tetrahedron Lett.* **2003**, *44*, 1883–1886. (d) Hamid, A.; Elomri, A.; Daich, A. *Tetrahedron Lett.* **2006**, *47*, 1777–1781. (e) Bowman, W. R.; Elsegood, M. R. J.; Stein, T.; Weaver, G. W. *Org. Biomol. Chem.* **2007**, *5*, 103–113.

(25) For recent syntheses of tryptanthrine, see: (a) Jahng, K. C.; Kim, S. I.; Kim, D. H.; Seo, C. S.; Son, J.-K.; Lee, S. H.; Lee, E. S.; Jahng, Y. *Chem. Pharm. Bull.* **2008**, *56*, 607–609. (b) Batanero, B.; Barba, F. *Tetrahedron Lett.* **2006**, *47*, 8201–8203. (c) See also: ref 21a.