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Mild and Direct Conversion of Quinoline *N*-Oxides to 2-Amidoquinolines with Primary Amides

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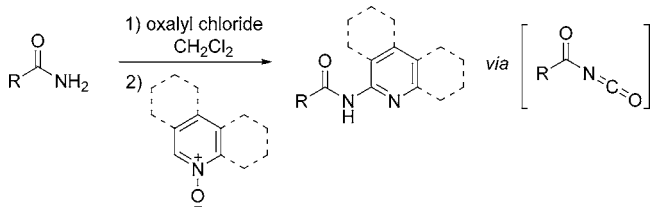
ABSTRACT



A simple, one-pot procedure is described for the direct conversion of quinoline *N*-oxides to α-amidoquinolines with primary amides. This methodology is complimentary to the Abramovich reaction, which is limited to the introduction of secondary amides via imidoyl chlorides. Although reaction conditions are quite similar, omission of the base is key for successful reaction with primary amides, which were found not to proceed through the intermediacy of an imidoyl chloride but rather through an acyl isocyanate.

N-Acylated 2-aminoquinolines are important constituents in pharmaceutical drug candidates,[1] and ubiquitously present in the patent literature.[2] They also have been shown to play an important role in molecular recognition processes.[3] One of the most direct means to access 2-aminoquinolines from quinolines is through α-amination with sodium or potassium amide, commonly referred to as the Chichibabin reaction.[4] Alternatively, conversion of quinoline *N*-oxides to 2-aminoquinolines can be achieved via 2-chloroquinolines, or more directly through *N*-oxide activation with TsCl[5] or dimethyl sulfate[6] followed by displacement with ammonia. In these previous cases, C-2 versus C-4 regioselectivity can be

(1) For recent examples, see: (a) Inglis, S.; Jones, R.; Fritz, D.; Stojkoski, C.; Booker, G.; Pyke, S. *Org. Biomol. Chem.* **2005**, *3*, 2543. (b) Gerster, J. F.; Lindstrom, K. J.; Miller, R. L.; Tomai, M. A.; Birmachu, W.; Bomersine, S. N.; Gibson, S. J.; Imbertson, L. M.; Jacobson, J. R.; Knafla, R. T.; Maye, P. V.; Nikolaides, N.; Oneyemi, F. Y.; Parkhurst, G. J.; Pecore, S. E.; Reiter, M. J.; Scribner, L. S.; Testerman, T. L.; Thompson, N. J.; Wagner, T. L.; Weeks, C. E.; Andre, J.-D.; Lagain, D.; Bastard, Y.; Lupu, M. *J. Med. Chem.* **2005**, *48*, 3481. (c) Jackson, S. A.; Sahni, S.; Lee, L.; Luo, Y.; Nieduzak, T. R.; Liang, G.; Chiang, Y.; Collar, N.; Fink, D.; He, W.: Laoui, A.; Merrill, J.; Boffey, R.; Crackett, P.; Rees, B.; Wong, M.; Guilloteau, J.-P.; Mathieu, M.; Rebello, S. S. *Bioorg. Med. Chem.* **2005**, *13*, 2723. (d) Benard, C.; Zouhiri, F.; Normand-Bayle, M.; Danet, M.; Desmaele, D.; Leh, H.; Mouscadet, J.-F.; Mbemba, G.; Thomas, C.-M.; Bonnenfant, S.; Le Bret, M.; d'Angelo, J. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2473. (e) Tavares, F. X.; Boncek, V.; Deaton, D. N.; Hassell, A. M.; Long, S. T.; Miller, A. B.; Payne, A. A.; Miller, L. R.; Shewchuk, L. M.; Wells-Knecht, K.; Willard, D. H., Jr.; Wright, L. L.; Zhou, H.-Q. *J. Med. Chem.* **2004**, *47*, 588. (f) Webb, T. R.; Lvovskiy, D.; Kim, S.-A.; Ji, X.-d.; Melman, N.; Linden, J.; Jacobson, K. A. *Bioorg. Med. Chem.* **2003**, *11*, 77. (g) Renau, T. E.; Leger, R.; Yen, R.; She, M. W.; Flamme, E. M.; Sangalang, J.; Gannon, C. L.; Chamberland, S.; Lomovskaya, O.; Lee, V. *J. Bioorg. Med. Chem. Lett.* **2002**, *12*, 763. (h) Brzozowski, Z.; Saczewski, F. *J. Med. Chem.* **2002**, *45*, 430. (i) Selwood, D. L.; Brummell, D. G.; Glen, R. C.; Goggin, M. C.; Reynolds, K.; Tatlock, M. A.; Wishart, G. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1089. (j) Colotta, V.; Catarzi, D.; Varano, F.; Cecchi, L.; Filacchioni, G.; Martini, C.; Trincavelli, L.; Lucacchini, A. *J. Med. Chem.* **2000**, *43*, 3118.

(2) A survey of patent literature spanning from 2000 to 2005 revealed over 90 cases.

(3) (a) Li, J.-S.; Gold, B. *J. Org. Chem.* **2005**, *70*, 8764. (b) Li, J.-S.; Chen, F.-X.; Shikiya, R.; Marky, L. A.; Gold, B. *J. Am. Chem. Soc.* **2005**, *127*, 12657. (c) Nakatani, K.; Sando, S.; Kumasawa, H.; Kikuchi, J.; Saito, I. *J. Am. Chem. Soc.* **2001**, *123*, 12650. (d) Nakatani, K.; Sando, S.; Saito, I. *J. Am. Chem. Soc.* **2000**, *122*, 2172.

(4) For a review on the Chichibabin reaction, see: McGill, C. K.; Rappa, A. *Adv. Heterocycl. Chem* **1988**, *44*, 1.

(5) (a) Miura, Y.; Takaku, S.; Fujimura, Y.; Hamana, M. *Heterocycles* **1992**, *34*, 1055. (b) Glennon, R. A.; Slusher, R. M.; Lyon, R. A.; Titeler, M.; McKenney, J. D. *J. Med. Chem.* **1986**, *29*, 2375.

(6) Storz, T. *Org. Proc. Res. Dev.* **2004**, *8*, 663.

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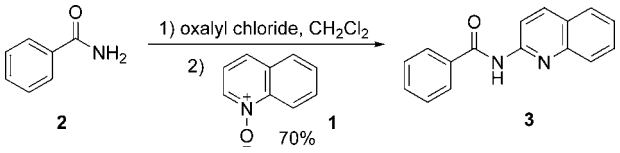
problematic, and an extra amidation step is then required to access 2-amidoquinolines.

In a recent development program of a drug candidate, we were seeking a more expeditious means to access 2-amidoquinolines. In literature precedents, Abramovich first reported direct formation of 2-amidoquinolines from quinoline *N*-oxides using isolated imidoyl chlorides.[7] Merck later developed a mild method for the generation of imidoyl chlorides and their subsequent in situ reaction with *N*-oxides.[8] These methods are limited to secondary amides, as chloroimidates of primary amides readily eliminate to the corresponding nitrile. To the best of our knowledge, the sole report of direct introduction of a primary amide onto quinoline *N*-oxide (**1**) was achieved by activation of the latter in neat benzoyl chloride at 175−180 °C in the presence of benzamide.[9] Due to the aforementioned reasons, a milder method to achieve this type of transformation would be highly desirable. Herein, we report a mild and general method for generating *N*-acylated quinolines from *N*-oxides using primary amides.

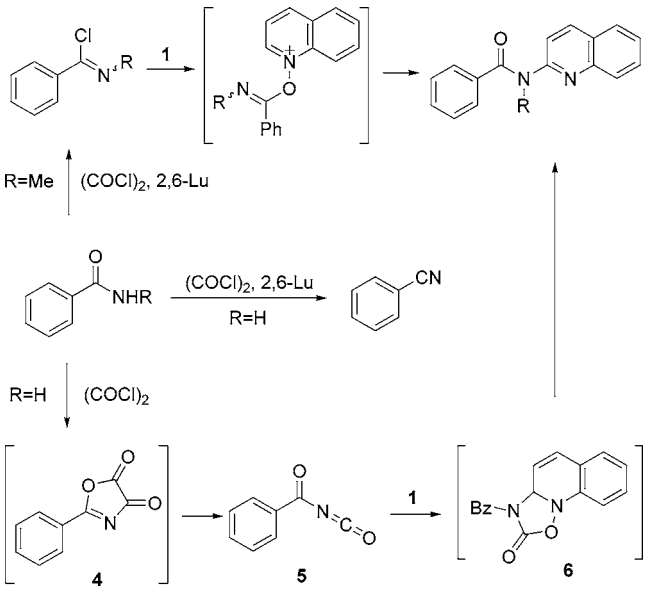
In a control experiment with the in situ imidoyl chloride formation procedure, treatment of benzamide (**2**) with oxalyl chloride in the presence of 2,6-lutidine not unexpectedly led to dehydration to form benzonitrile. However, when this reaction was performed in the absence of base, we found it to generate the previously elusive 2-benzamidoquinoline (**3**) in 70% yield (Scheme 1).

Scheme 1. Mild and Regiospecific 2-Benzamidation of Quinoline *N*-oxide



In essence, primary amides can be introduced onto quinolines by using essentially the same procedure reported for secondary amides, but in the absence of base. In contrast to the original procedure, however, the reaction does not proceed through the intermediacy of an imidoyl chloride. Closer inspection by ^{1}H and ^{13}C NMR reveals that omission of the lutidine base changes the sequence of events such that unstable 2-phenyloxazoline-4,5-dione hydrochloride (**4**) is initially formed which then converts to benzoyl isocyanate (**5**).[10,11] The latter then undergoes a 1,3-dipolarcycloaddition with quinoline *N*-oxide followed by decarboxylative aromatization of the adduct leading to 2-benzamidoquinoline (Scheme 2).[12]

Scheme 2. Reaction Pathways



The generality of this reaction was then investigated. As a matter of convenience, commercially available benzoyl isocyanate[13] (**5**) was employed to evaluate the substrate scope of various pyridine *N*-oxide derivatives (Table 1). In the following experiments, 2 equiv of isocyanate were used due to the hygroscopic nature of the pyridine *N*-oxides partners and the potency of the technical grade isocyanate employed.[14] As anticipated from our original results, reaction of benzoyl isocyanate (**5**) with quinoline *N*-oxide (**1**) proceeded in refluxing dichloromethane and provided 2-benzamidoquinoline (**3**) in 77% yield. Electron withdrawing substituted quinolines *N*-oxides were also converted to their corresponding 2-benzamidoquinolines in similar times and yields (entries 3 and 5). However, electron-rich 6-methoxyquinoline *N*-oxide (**15**) required more forceful conditions where 5 equiv of isocyanate **5** were required to reach reaction completion after 40 h at reflux. It is noteworthy that all the aforementioned reactions proceeded with the expected regiospecificity. Isoquinoline *N*-oxide (**7**) showed increased reactivity toward

(7) (a) Abramovich, R. A.; Singer, G. M. *J. Am. Chem. Soc.* **1969**, *91*, 5672. (b) Abramovich, R. A.; Singer, G. M. *J. Org. Chem.* **1974**, *39*, 1795. (c) Abramovich, R. A.; Rogers, R. B. *J. Org. Chem.* **1974**, *39*, 1802. (d) Abramovich, R. A.; Pilski, J.; Konitz, A.; Tomasik, P. *J. Org. Chem.* **1983**, *48*, 4391.

(8) Manley, P. J.; Bilodeau, M. T. *Org. Lett.* **2002**, *4*, 3127.

(9) Kurbatov, Y. V.; Solekhova, M. A. *Zh. Org. Khim.* **1981**, *17*, 1121.

(10) Compound **4**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.65 (br s, 1H), 7.93 (d, J = 7.5 Hz, 2H), 7.68 (t, J = 7.5 Hz, 1H), 7.55 (t, J = 7.5 Hz, 2H). Compound **5**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 7.5 Hz, 2H), 7.64 (t, J = 7.5 Hz, 1H), 7.48 (t, J = 7.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.38, 159.31, 135.02, 130.77, 129.06, 129.02.

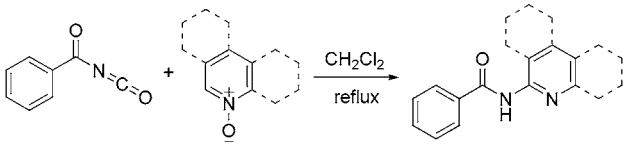
(11) (a) Speziale, A. J.; Smith, L. R. *J. Org. Chem.* **1962**, *27*, 3742. (b) Speziale, A. J.; Smith, L. R. *J. Org. Chem.* **1963**, *28*, 1805.

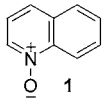
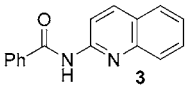
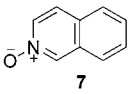
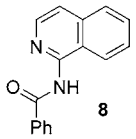
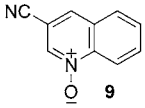
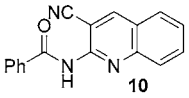
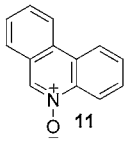
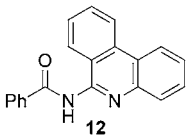
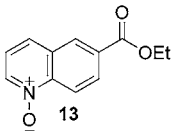
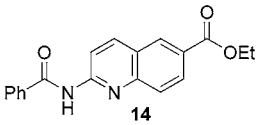
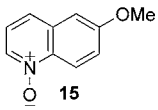
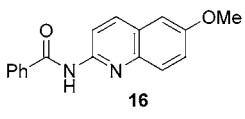
(12) For an isolated example of reacting benzoylisocyanate with 1*H*-imidazo[4,5-*c*]quinoline 5*N*-oxide, see: Gerster, J. F. U.S. Patent 5,175,296, 1992.

(13) Purchased as technical grade material (90%) from Aldrich Chemical Co.

(14) **General procedure with benzoyl isocyanate:** To a stirred solution of quinoline *N*-oxide (5.0 mmol) in dichloromethane (15 mL) at room temperature was added a solution of benzoyl isocyanate (10.0 mmol) in dichloromethane (5 mL). The resulting mixture was heated to reflux except for phenanthridine *N*-oxide and isoquinoline *N*-oxide which were kept at room temperature. Upon reaction completion, the reaction was quenched with methanol (500 μL), stirred for 15 min, and then concentrated under vaccum. Unless otherwise noted (see the Supporting Information), the residual material was purified by chromatography to yield the desired benzamidoquinoline.

Table 1. Direct Benzamidation of Quinoline *N*-oxides with Benzoyl Isocyanate



entry	*N*-oxide	reaction time	product	yeild (%)[a]
1	 **1**	20 h	 **3**	77
2	 **7**	3 h[b]	 **8**	97
3	 **9**	32 h	 **10**	91
4	 **11**	2 min[b]	 **12**	99
5	 **13**	22 h	 **14**	82
6	 **15**	40 h[c]	 **16**	62

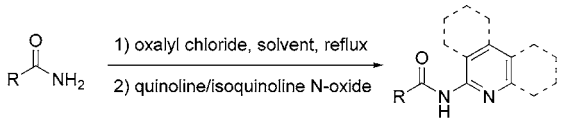
[a] Isolated yields. [b] Reaction performed at room temperature. [c] 5 equiv of benzoyl isocyanate required.

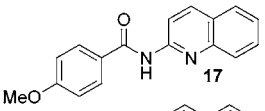
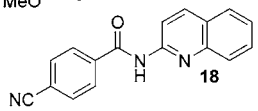
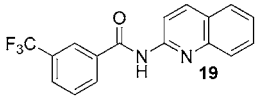
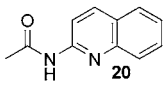
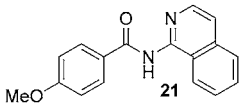
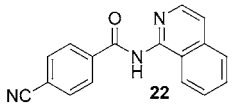
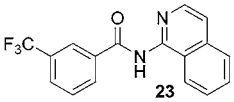
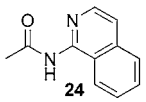
benzoyl isocyanate (**5**) as compared to quinoline *N*-oxide (**1**) by proceeding at room temperature and reaching completion in 3 h. The compound produced in 97% yield was identified as 1-benzamidoisoquinoline (**8**); none of the 3-regioisomer was detected. Reaction with phenanthridine *N*-oxide (**11**) proceeded even more readily by reaching completion within 2 min. Unfortunately, reactions with pyridine *N*-oxides were nonproductive as they catalyzed the cyclotrimerization of benzoyl isocyanate to tribenzoyl isocyanurate, consistent with literature precedent.[15]

The substrate scope of various primary amides was then investigated on quinoline *N*-oxide (**1**) and isoquinoline *N*-oxide (**7**). The requisite isocyanate formations were first monitored by ^{13}C NMR to determine reaction time and temperature required for this initial process to reach complete conversion. Whereas benzamide (**2**) and substituted aryl amides all converted to the corresponding isocyanates within 1 h in refluxing dichloromethane (entries 1−3), acetamide required more forcing conditions (2.5 h in refluxing 1,2-dichloroethane; entry 4).

In accordance with previous reactions, the cycloadditions/decarboxilative rearangements were performed under reflux with quinoline *N*-oxide (**1**) and at room temperature with isoquinoline *N*-oxide (**7**).[16] As exemplified in Table 2,

Table 2. Direct Amidation of Quinoline and Isoquinoline *N*-Oxides with Various Amides



entry	solvent	activation time	rxn time	product	yeild (%)[a]
1	CH_2Cl_2	50 min	24 h[b]	 **17**	79
2	CH_2Cl_2	40 min	24 h[b]	 **18**	74
3	CH_2Cl_2	60 min	16 h[b]	 **19**	81
4	$(ClCH_2)_2$	2.5 h	1.5 h[b]	 **20**	83
5	CH_2Cl_2	50 min	20 h[c]	 **21**	82
6	CH_2Cl_2	40 min	40 min[c]	 **22**	64
7	CH_2Cl_2	60 min	2 h[c]	 **23**	91
8	$(ClCH_2)_2$	2.5 h	24 h[c]	 **24**	94

[a] Isolated yields. [b] Reaction performed at reflux. [c] Reaction performed at room temperature.

reaction completion on all the cases studied was achieved within 24 h, and provided the desired amidoquinoline in

(15) Tsuge, O.; Mizuguchi, R. *Nippon Kagaku Zasshi* **1965**, *86*, 325.

(16) **General amidation procedure starting from amides:** To a stirred solution of amide (10.0 mmol) in dichloromethane (10 mL) was added oxalyl chloride (10.0 mmol) dropwise at room temperature. The reaction mixture was stirred at room temperature, then heated to reflux until isocyanate formation is complete. The foregoing solution was added to a solution of quinoline *N*-oxide or isoquinoline *N*-oxide (5.0 mmol) in dichloromethane (10 mL). The resulting mixture was heated to reflux except for reactions with isoquinoline *N*-oxide which were performed at room temperature. Upon reaction completion, the reaction was quenched with methanol (500 μL), stirred for 15 min, and then concentrated under vaccum. Unless otherwise noted, the residual material was purified by chromatography to yield the desired amidoquinoline.

generally good yields. Also, the reactions exhibited high degrees of selectivity as no other regioisomers were detected in the reaction mixtures.

In conclusion, we have developed a novel, mild, and straightforward procedure for the regioselective introduction of primary amides onto quinolines and derivatives via acylisocyanates. This methodology is complimentary to the Abramovich reaction, which is limited to the introduction of secondary amido functionality via imidoyl chlorides. Due to the ubiquity of *N*-acylated 2-aminoquinolines in pharmaceutical drug candidates, this methodology should prove useful for the synthesis of compounds bearing such substructures.

Supporting Information Available: Experimental details for the synthesis of amidoquinolines with corresponding ^{1}H and ^{13}C NMR. This material is available free of charge via the Internet at http://pubs.acs.org.

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