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PII: S0040-4039(14)00470-5
DOI: http://dx.doi.org/10.1016/j.tetlet.2014.03.061
Reference: TETL 44383

To appear in: *Tetrahedron Letters*

Received Date: 1 February 2014
Revised Date: 9 March 2014
Accepted Date: 13 March 2014

Please cite this article as: Kobayashi, Y., Suzuki, Y., Ogata, T., Kimachi, T., Takemoto, Y., A diversity-oriented synthesis of caroverine derivatives via TEMPO-promoted aerobic oxidative C–N bond formation, *Tetrahedron Letters* (2014), doi: http://dx.doi.org/10.1016/j.tetlet.2014.03.061

A diversity-oriented synthesis of caroverine derivatives via TEMPO-promoted aerobic oxidative C–N bond formation

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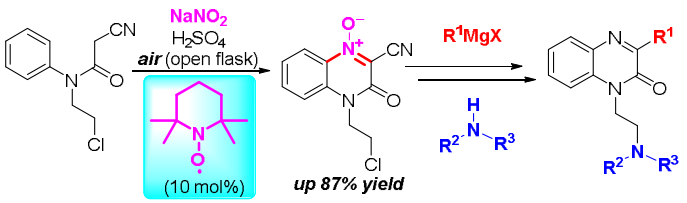
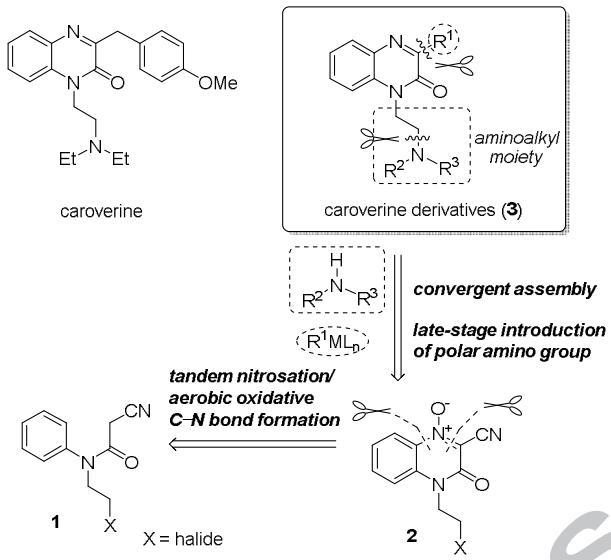
Abstract: A concise method has been developed for the synthesis of caroverine and its derivatives. The quinoxalinone scaffold of these compounds was constructed via the tandem nitrosation/aerobic oxidative C–N bond formation reaction of *N*-(2-chloroethyl)-2-cyano-*N*-phenylacetamide, followed by sequential Grignard, Finkelstein and nucleophilic substitutions reactions to give several different derivatives. Herein, we describe the development of this strategy in terms of the optimization of each step as well as the effect of different additives on the individual reactions.

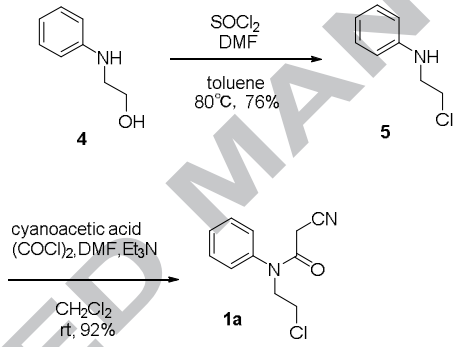


Keywords: quinoxaline, organocatalyst, heterocycles, nitroxyl radical

Carbon–nitrogen bond forming reactions are one the most fundamental transformations in organic synthesis.[1] During the last few decades, there has been an increase in the number of reports pertaining to the development of direct C–H functionalization/C–N bond forming methodologies, with particular emphasis on atom economy.[2] Oxidative transformations of this type have also recently been elaborated to include metal-free reactions,[3] as well as reactions involving inexpensive oxidants such as molecular oxygen,[4] where they have been used to provide efficient approaches to a variety of interesting nitrogen-containing heterocycles.[2–4] As part of our previous study,[5,6] we reported the tandem nitrosation/aerobic oxidative C–N bond formation reaction of cyanoacetanilides **1**, to give the corresponding quinoxalinones **2**,[5] which were successfully applied to the synthesis of biologically important compounds, such as ataquimast[7] and opaviralne.[8] It was envisaged that this method could also be applied to the diversity-oriented synthesis (DOS)[9] of caroverine and its derivatives (Scheme 1). Caroverine itself is a spasmolytic and inner-ear-protective agent, as well as a potent antioxidant.[10] Aminoalkyl moieties can be found in wide range of pharmaceutical agents, where they generally make a significant contribution to the pharmacological activity.[11] For this reason, we designed a new strategy for the DOS of caroverine derivatives **3** involving the introduction of a variety of different amino groups to the halide **2** with the aim of establishing a detailed structure-activity relationship (SAR). It was envisaged that the CN group of **2** could be substituted with organometallic reagents,[5] enabling further derivatization. Furthermore, the late stage introduction of the polar amino group would avoid any difficulties associated with the preparation and isolation of compounds **1** and **2**. Herein, we report the development of a DOS strategy for the construction of **3** using the tandem nitrosation/aerobic oxidative C–N bond forming reaction of cyanoacetanilides **1** as the key step, with 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) being used to promote the oxidative C–N bond-forming step.



Scheme 1. Strategy for the synthesis of caroverine derivatives

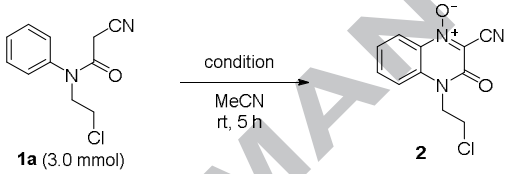


Scheme 2. Preparation of cyanoacetanilide **1**

First, we attempted to establish a method for the synthesis of the cyanoacetanilide bearing a halide as a leaving group (Scheme 2). The treatment of the commercially available *N*-hydroxyethylaniline (**4**) with $SOCl_2$ gave the corresponding chloride **5**, which was subjected to an amidation reaction with 2-cyanoacetyl chloride to give the chloro-substituted anilide **1a** in good yield (70% in 2 steps).[6] With the anilide in hand, we proceeded to investigate the tandem nitrosation/aerobic oxidative C–N bond forming reaction of **1a** (Table 1). Unfortunately, the use of five equivalents of $NaNO_2$ and H_2SO_4 in MeCN gave the desired product **2** in a low yield of 20% (Table 1, entry 1). We hypothesized that the low yield of **2** occurred

as a consequence of the oxidation step (vide infra), with it not being possible for the substrate to interact efficiently with the oxidant (gaseous NO_2). Given that NO_2 and nitroxyl radicals have been used previously for the oxidation of alcohols,[12] we conducted the reaction in the presence of TEMPO (10 mol%) and found that the chemical yield was significantly improved to 87% (Table 1, entry 2). However, our efforts to reduce the amount of $NaNO_2$ and H_2SO_4 were unsuccessful (Table 1, entries 3 and 4). The optimized condition shown in entry 2 was successfully applied to the gram-scale (4.9 g) synthesis of **2** in 77% yield (Table 1, entry 5).

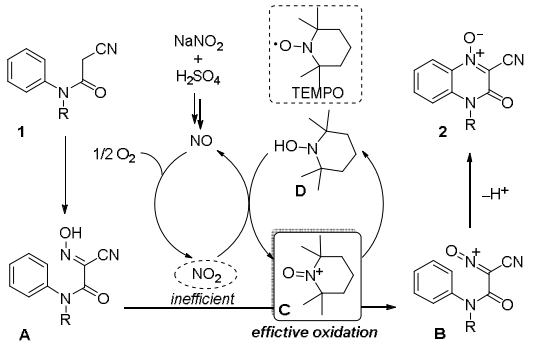
Table 1. Tandem nitrosation/aerobic oxidative C–N bond formation of **1a**



Entry	Conditions	TEMPO (equiv)	Yield[a] (%)
1	$NaNO_2$ (5.0 equiv), H_2SO_4 (5.0 equiv)	–	20
2	$NaNO_2$ (5.0 equiv), H_2SO_4 (5.0 equiv)	0.1	87
3	$NaNO_2$ (3.0 equiv), H_2SO_4 (3.0 equiv)	0.1	65
4	$NaNO_2$ (2.0 equiv), H_2SO_4 (2.0 equiv)	0.1	43
5[b]	$NaNO_2$ (5.0 equiv), H_2SO_4 (5.0 equiv)	0.1	77

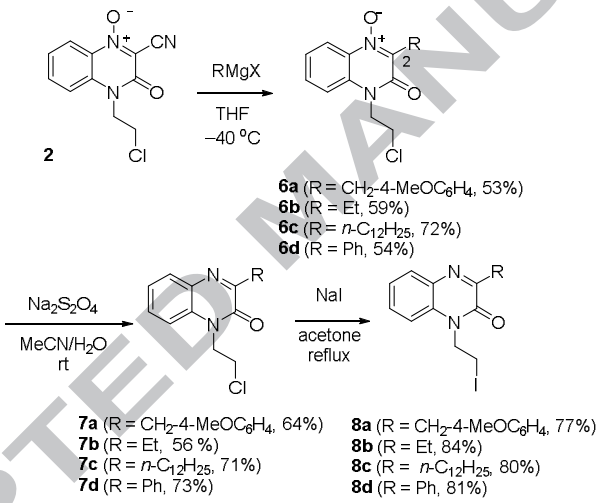
[a]Isolated yield.

[b]The reaction was performed on 25 mmol scale.



Scheme 3. A plausible promoting effect of TEMPO

A plausible mechanism to account for the promoting effect of TEMPO is shown in Scheme 3. According to this mechanism, the active methylene of **1** would be nitrosated and isomerized to give oxime-type intermediate **A**, which would be oxidized to give the *N*-oxonitrenium intermediate **B**.[5] It was envisaged that the NO_2 generated *in situ* would behave as the oxidant under the original reaction conditions,[5] although this system was found to be inefficient when **1a** was used as the substrate. In contrast, TEMPO and/or its oxidized form **C** would interact more effectively with intermediate **A** to afford **B**, and the resulting reduced form **D** would be immediately oxidized by NO_2 to afford **C**.[12,13] Finally, the cyclization of **B** would give the desired product **2**.

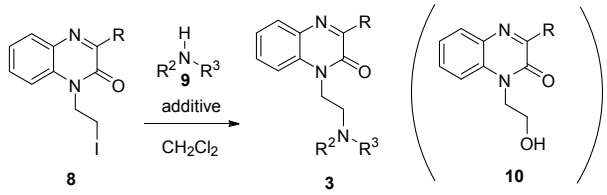


Scheme 4. Substitution of CN group utilizing Grignard reagents

With a robust method for the preparation of **2** in hand, we proceeded to investigate the substitution of the CN group with a variety of different carbon nucleophiles (Scheme 4). As expected, several commercially available Grignard reagents reacted with **2** to afford the corresponding quinoxalinone-*N*-oxides **6** bearing different substituents at the C2 position in yields of 53–72%. Subsequent reductive cleavage of the *N*-oxides **6** with $Na_2S_2O_4$[14] gave the chlorides **7**,[15] which were converted to the corresponding iodides in high yields (77–84%) using a Finkelstein Reaction.[16] These compounds were now ready for the

final substitution reaction to give the target compounds.

Table 2. Introduction of various amino groups



Entry	**8** (R)	**9** (R^2, R^3)	Additive	**3** (Yield, %)[a]
1	**8a** (CH_2-4-$MeOC_6H_4$)	**9A** (Et, Et)	–	**3aA** (0)[b]
2	**8a**	**9A**	TBSCl (1.0 equiv)	**3aA** (90)
3	**8a**	**9B** (-$CH_2CH_2CH_2CH_2$-)	TBSCl (1.0 equiv)	**3aB** (quant.)
4	**8a**	**9C** (-$CH_2CH_2CH_2CH_2CH_2$-)	TBSCl (1.0 equiv)	**3aC** (93)
5	**8a**	**9D** (-$CH_2CH_2OCH_2CH_2$-)	TBSCl (1.0 equiv)	**3aD** (57)
6	**8b** (Et)	**9A**	TBSCl (1.0 equiv)	**3bA** (70)
7	**8c** (*n*-$C_{12}H_{25}$)	**9A**	TBSCl (1.0 equiv)	**3cA** (78)
8	**8d** (Ph)	**9A**	TBSCl (1.0 equiv)	**3dA** (82)

[a]Isolated yield.

[b] **10** was obtained in 68% yield.

To complete this work, we investigated the nucleophilic substitution of the alkyl iodide in compound **8** with a range of secondary amines (Table 2). Disappointingly, the use of diethylamine (**9A**) as the nucleophilic amine did not afford any of the desired product **3aA**, with the undesired alcohol **10** being isolated instead in 68% yield (Table 2, entry 1). This product was most likely formed via the intramolecular substitution of the alkyl iodide moiety of **8a** with the oxygen atom of the amide moiety followed by hydration. When the reaction was conducted in the presence *tert*-butyldimethylchlorosilane (TBSCl),[17] the desired product **3aA** was formed in 90% yield (Table 2, entry 2). This amination protocol was also successfully applied to a range of different secondary amines, including prrolidinyl-, piperidinyl, and morpholinyl amines, with the corresponding products **3aB**–**aD** being formed in good to excellent yields (Table 2, entries 3–5). To expand the scope of this transformation even further, it was also applied to the synthesis of the caroverine derivatives **3bA** and **3cA**,

bearing different R groups, which were synthesized from **8b–d** in 70–82% yields (Table 2, entries 6–8).

In conclusion, we have demonstrated that the tandem nitrosation/aerobic oxidative C–N bond forming reaction of **1a** can be used to provide facile access to caroverine derivatives. We have also shown that TEMPO can be used an effective catalyst to promote the oxidative C–N bond forming step, and that TBSCl could be used to inhibit the hydrolysis of the alkyl iodide moiety during the final nucleophilic substitution step. We believe that these finding could be useful for the synthesis of other quinoxalinone derivatives, as well as the development of the related C–N bond forming reactions, which we are currently investigating in our laboratory.

References and notes

1. For reviews, see: (a) Jiang, L.; Buchwald, S. L. *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; Wiley-VCH: Weinheim, 2004; Vol. 2, p699. (b) Hartwig, J. F. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley-Interscience: New York, 2002; p1051. (c) Surry, D. S.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 6338.

2. For pioneering work, see: (a) Tsang, W. C. P.; Zheng, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 14560. (b) Tsang, W. C. P.; Munday, R. H.; Brasche, G.; Zheng, N.; Buchwald, S. L. *J. Org. Chem.* **2008**, *73*, 7603.

3. For a recent review, see: Samanta, R.; Matcha, K.; Antonchick, A. P. *Eur. J. Org. Chem.* **2013**, 5769.

4. For selected recent reviews, see: (a) Wendlandt, A. E.; Suess, A. M.; Stahl, S. S. *Angew. Chem., Int. Ed.* **2011**, *50*, 11062. (b) Wertz, S.; Studer, A. *Green Chem.* **2013**, *15*, 3116. (c) Chiba, S. *Bull. Chem. Soc. Jpn.* **2013**, *86*, 1400.

5. Kobayashi, Y.; Kuroda, M.; Toba, N.; Okada, M.; Tanaka, R.; Kimachi, T. *Org. Lett.*, **2011**, *13*, 6280.

6. For our previous work using cyanoacetanilides, see: (a) Kobayashi,Y.; Harayama, T. *Org. Lett.* **2009**, *11*, 1603. (b)

Kobayashi, Y.; Harayama, T. *Tetrahedron Lett*. **2009**, *50*, 6665. (c) Kobayashi, Y.; Katagiri, K.; Azumaya, I.; Harayama, T. *J. Org. Chem*. **2010**, *75*, 2741. (d) Kobayashi, Y.; Nakatani, T.; Tanaka, R.; Okada, M.; Torii, E.; Harayama, T.; Kimachi, T. *Tetrahedron* **2011**, *67*, 3457. (e) Kobayashi,Y. *YakugakuZasshi* **2011**, *131*, 1037.

7. Patoisear, J.-F.; Tarayre, J.-P.; Autin, J.-M. PCT Int. Appl. WO9626928 A1 19960906, 1996.

8. (a) Roesner, M.; Billhardt-Troughton, U.-M.; Kirsch, R.;Kleim, J.-P.; Meichsner, C.; Riess, G.; Winkler, I. Eur. Pat. Appl. EP708093 A1 19960424, 1996. (b) Balzarini, J.; De Clercq, E.; Carbonez, A.; Burt, V.; Kleim, J.-P. *AIDS Res. Hum. Retroviruses* **2000**, *16*, 517. (c) Cass, L. M.; Moore, K. H. P.; Dallow, N. S.; Jones, A. E.; Sisson, J. R.; Prince,W. T. *J. Clin. Pharmacol*. **2001**, *41*, 528.

9. Burke, M. D.; Schreiber, S. L. *Angew. Chem. Int. Ed*. **2004**, *43*, 46.

10. (a) Udilova, N.; Kozlov, A. V.; Bieberschulte, W.; Frei, K.; Ehrenberger, K.; Nohl, H. *Biochem. Pharmacol*. **2003**, *65*, 59. (b) Nohl, H.; Bieberschulte, W.; Dietrich, B.; Udilova, N.; Kozlov, A.V. *BioFactors* **2003**, *19*, 79.

11. For selected recent examples, see: (a) Ruchelman, A. L.; Houghton, P. J.; Zhou, N.; Liu, A.; Liu, L. F.; LaVoie, E. J. *J. Med. Chem*. **2005**, *48*, 792. (b) Alcalde, E.; Mesquida, N.; López-Pérez, S.; Frigola, J.; Mercè, R. *J. Med. Chem*. **2009**, *52*, 675.

12. (a) Liu, R.; Liang, X.; Dong, C.; Hu, X. *J. Am. Chem. Soc*. **2004**, *126*, 4112. (b) Uyanik, M; Fukatsu, R.; Ishihara, K. *Chem. Asian J*. **2010**, *5*, 456. (c) Shibuya, M.; Osada, Y.; Sasano, Y.; Tomizawa, M.; Iwabuchi, Y. *J. Am. Chem. Soc*. **2011**, *133*, 6497.

13. This reaction was performed under in an open flask, because the reaction was unsuccessful when it was conducted in the presence of a catalytic amount of $NaNO_2$, even under an oxygen atmosphere. This difference in the outcome was attributed to the gradual release of NO_x from of the open flask. Details of the experimental process are provided in the Supplementary

Data section. The reaction promoting effect of TEMPO using several different substrates has also been described in the Supplementary Data section.

14. Note that a fresh $Na_2S_2O_4$ should be used for the reduction reaction. The use of an old bottle of this material led to a significant decrease of in the chemical yield of the reaction.

15. Very little product was obtained when chloride **7** was subjected to the nucleophilic substitution reaction with secondary amines **9**.

16. Landini, D.; Albanese, D.; Mottadelli, S.; Penso, M. *J. Chem. Soc., PerkinTrans. 1*, **1992**, 2309.

17. TBSCl was selected as the additive because the use of $TMSNEt_2$ as a nucleophile in the substitution reaction gave **3aA** in 87% yield.

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