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# Hexamethyldisilazane-iodine induced intramolecular dehydrative cyclization of diamides: a general access to natural and unnatural quinazolinones

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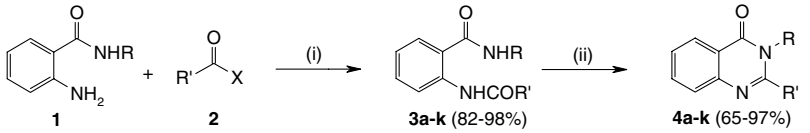
**Abstract**—A simple and efficient general approach to various quinazolinone scaffolds, including peptidomimetic examples, has been demonstrated by employing HMDS/$I_2$ for the intramolecular dehydrative cyclization of diamides. The protecting groups –Boc, –Fmoc and –Cbz tolerated the present reaction conditions and we did not observe any racemization. The present protocol has also been used as a key step for the efficient four-step syntheses of the naturally occurring quinazolinones, sclerotigenin, (−)-circumdatin-F and (−)-fumiquinazoline-F.


Quinazolinones are an important class of compounds and a large number of natural and unnatural quinazolinone skeletons with a variety of substituents have been prepared via several synthetic strategies, owing to the wide range of biological activities that they possess.[1] Retrosynthetically, intramolecular dehydrative cyclization of suitably substituted *N*-benzoylanthranilamides constitutes a concise and biomimetic route to all types of quinazolinone alkaloids.[1] However, previous conditions reported for such a dehydration are harsh and are suitable only for dehydrative cyclizations of unhindered 2,3-disubstituted-quinazolin-4-ones.[2] Quinazolinone based natural products demanding more structurally complex precursors have been constructed indirectly via thioamide formation,[3] oxidation of dehydroquinazolinone,[4] aza-Wittig condensations[5] or starting from the benzoxazinones.[6] Recently, a two-step approach for such a dehydration of diamides has been developed using $PPh_3/I_2/EtN(i\text{-}Pr)_2$ (Wipf's protocol)[7] to form the benzoxazine intermediate, followed by piperidine induced rearrangement to the target molecules.[8] The above approach has been successfully applied by different research groups for the synthesis of several complex bioactive natural quinazolinones.[7–9] These studies indicate that the development of a straightforward and efficient approach to natural and unnatural quinazolinones, more specifically for peptidomimetic examples bearing a variety of protecting groups, is a useful and challenging task of current interest. In continuation of our studies,[10] we herein report a new, facile and general approach to natural and unnatural quinazolinones (Schemes 1 and 2).

Anthranilamides **1** were prepared in very good yields from the reactions of isatoic anhydride/sulfinamide anhydride with a variety of primary amines using known




**Scheme 1.** Synthesis of unnatural quinazolinones and precursors of natural quinazolinones.

*Keywords*: Diamides; HMDS/$I_2$; Intramolecular dehydrative cyclizations; Natural and unnatural quinazolinones; Synthesis.
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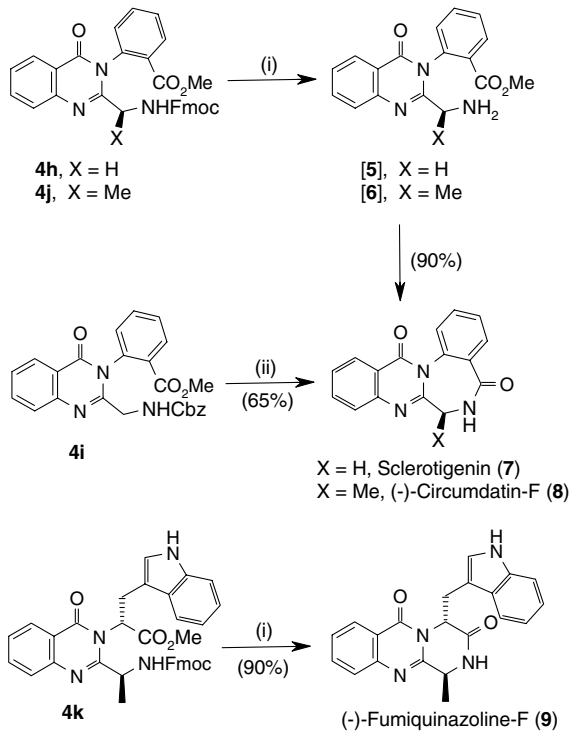



**Scheme 2.** Reagents and conditions: (i) Piperidine in DCM (20%), rt, 15 min (90%); (ii) (a) HBr in AcOH (33%), 60 °C, 1 h; (b) $SiO_2$, TEA, AcOEt, rt, 12 h (65%).

procedures.[9b,c] Intermediates **3a**–**k** were prepared by condensing anthranilamides **1** with the appropriate acid chlorides/carboxylic acids **2** in 82–98% yield (Scheme 1, Table 1, entries 1–11). Compounds **3a**,**b** in DCM did not undergo reaction on treatment with cyanuric chloride/triethylamine, chlorotrimethylsilane/iodine and diethylazodicarboxylate/triphenylphosphine. We felt that the cheap and readily available hexamethyldisilazane (HMDS) would be a better reagent to induce the intramolecular dehydrative cyclizations of **3a**–**k** to obtain quinazolinones **4a**–**k** via the highly regioselective silylation of the more reactive anilide carbonyl oxygen, followed by deoxysilylation. To our delight, treatment of **3a**,**b** with HMDS/$ZnCl_2$ in benzene solution under reflux (Vorbruggen's protocol)[11] furnished the desired products **4a**,**b** in ~100% yields. However, in our hands, treatment of peptidomimetic precursor **3d** with HMDS/$ZnCl_2$ resulted in the formation of a complex reaction mixture, while **3j** did not react under the same conditions. We envisaged[12] that the use of the soft Lewis acid iodine in place of the borderline Lewis acid zinc chloride would result in efficient conversion of **3a**–**k** to **4a**–**k**. Rewardingly, the reactions of **3a**–**i** with HMDS/$I_2$ in DCM at room temperature furnished the desired quinazolinones **4a**–**i** in 65–97% yields (entries 1–9). However, compounds **3j**,**k** in DCM at room temperature, or under reflux conditions, were reluctant to react with HMDS/$I_2$, while the same reactions in refluxing chloroform furnished the desired compounds **4j**,**k** in 55/41% yields and in refluxing benzene furnished compounds **4j**,**k** in 75/65% yields, respectively (entries 10 and 11), revealing that a higher temperature was necessary for those two intramolecular dehydrative cyclizations. For the conversion of **3a**–**k** to **4a**–**k**, we noticed that an increase in the molar equivalents of HMDS and iodine reduced the reaction time with an improvement in the

**Table 1.** Conversion of anthranilamides **1** to diamides **3** and quinazolinones **4**

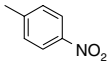
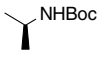
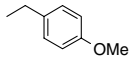
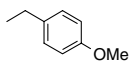
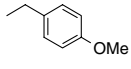
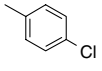
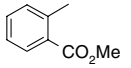
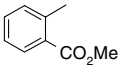
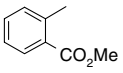
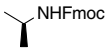
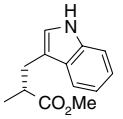
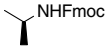
| Entry | –R | –R′ | –X | Conditions (i) | Product (yield) | Conditions (ii)[a] | Product (yield, %) |
|---|---|---|---|---|---|---|---|
| 1 |  | $-CH_2CH_3$ | Cl | TEA, DCM, rt, 8 h | **3a** (98) | HMDS (1.5), $I_2$ (0.5), DCM, rt, 30 min | **4a** (93) |
| 2 |  |  | Cl | TEA, DCM, rt, 10 h | **3b** (97) | HMDS (1.5), $I_2$ (0.5), DCM, rt, 30 min | **4b** (95) |
| 3 |  |  | Cl | TEA, DCM, rt, 12 h | **3c** (86) | HMDS (2.0), $I_2$ (1.0), DCM, rt, 4 h | **4c** (86) |
| 4 |  |  | OH | EDCI,[b] HOBT,[c] DCM, rt, 16 h | **3d** (82) | HMDS (3.0), $I_2$ (0.7), DCM, rt, 4 h | **4d** (70) |
| 5 |  | $-CH_2CH_3$ | Cl | TEA, DCM, rt, 12 h | **3e** (96) | HMDS (1.5), $I_2$ (0.5), DCM, rt, 3 h | **4e** (97) |
| 6 |  |  | Cl | TEA, DCM, rt, 12 h | **3f** (90) | HMDS (1.5), $I_2$ (0.5), DCM, rt, 7 h | **4f** (96) |
| 7 |  |  | Cl | TEA, DCM, rt, 14 h | **3g** (85) | HMDS (2.0), $I_2$ (1.0), DCM, rt, 5 h | **4g** (90) |
| 8 |  | $-CH_2NHFmoc$ | Cl | Aq. $Na_2CO_3$, DCM, rt, 1 h | **3h** (96) | HMDS (3.0), $I_2$ (3.0), DCM, rt, 4 h | **4h** (75) |

**Table 1** (*continued*)

| Entry | –R | –R′ | –X | Conditions (i) | Product (yield) | Conditions (ii)[a] | Product (yield, %) |
|---|---|---|---|---|---|---|---|
| 9 |  | $-CH_2NHCbz$ | OH | EDCI, DCM, rt, 16 h | **3i** (82) | HMDS (4.0), $I_2$ (3.0), DCM, rt, 4 h | **4i** (65) |
| 10 |  |  | Cl | Aq. $Na_2CO_3$, DCM, rt, 1 h | **3j** (95) | HMDS (5.0), $I_2$ (4.0), benzene, reflux, 4 h | **4j** (75) |
| 11 |  |  | Cl | Aq. $Na_2CO_3$, DCM, rt, 1 h | **3k** (90) | HMDS (5.0), $I_2$ (4.0), benzene, reflux, 3 h | **4k** (65) |

[a] HMDS and $I_2$ equivalents used are indicated in brackets.
[b] *N*-Ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide.
[c] Use of HOBT was necessary to avoid racemization.

yields (Table 1). The protecting groups –Boc, –Fmoc and –Cbz tolerated the present reaction conditions and in addition, we did not observe any racemization.

In the present reaction, the formation of **4a** was not observed even in trace amounts in the absence of either HMDS or iodine and the presence of a catalytic amount of iodine was necessary to induce the first silylation of the more reactive amide carbonyl group, which was followed by in situ ring closure with deoxysilylation.

Finally, the piperidine induced deprotection of the protecting group Fmoc in **4h**,**j** led to unisolable amino-ester intermediates **5**,**6** which on in situ intramolecular cyclization furnished the natural products sclerotigenin (**7**)[6a] and (−)-circumdatin-F (**8**)[9c] in 90% yields (Scheme 2). Similarly **4k**, also on Fmoc deprotection, directly furnished (−)-fumiquinazoline-F (**9**)[9e] in 90% yield. Quinazolinone **4i** on treatment with 33% HBr in acetic acid at 60 °C for one hour furnished the corresponding hydrobromide salt of the amino-ester intermediate, which on treatment with triethylamine in ethyl acetate at room temperature furnished sclerotigenin (**7**) in 65% yield via an instantaneous intramolecular cyclization pathway. The natural quinazolinones **7**–**9** were obtained in four steps with very good overall yields and the analytical and spectral data obtained for **7**–**9** were in complete agreement with the reported data.[6a,9c,e]

In summary, we have demonstrated a simple and efficient general approach to various quinazolinone scaffolds, for the first time by employing HMDS/$I_2$ for the intramolecular dehydrative cyclization of diamides. We feel that our approach will be useful for the design of libraries of quinazolinone congeners for structure-activity relationship studies. Studies on the synthesis of the asperlicin-family of quinazolinones using the present method are in progress in our laboratory.

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## Supplementary data

Experimental procedures for the synthesis of compounds **3**, **4**, **7**, **8** and **9** along with analytical and spectral data are included. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.03.032.

## References and notes

1. (a) Mhaske, S. B.; Argade, N. P. *Tetrahedron* **2006**, *62*, 9787; (b) Michael, J. P. *Nat. Prod. Rep.* **1997**, *14*, 605–618, and references cited therein.
2. (a) Roy, A. D.; Subramanian, A.; Roy, R. *J. Org. Chem.* **2006**, *71*, 382–385; (b) Brown, D. J. *Quinazolines. Supplement I*; Wiley: New York, 1996; (c) Buchi, G.; DeShong, P. R.; Katsumura, S.; Sugimura, Y. *J. Am. Chem. Soc.* **1979**, *101*, 5084–5086; (d) Ohnuma, T.; Kimura, Y.; Ban, Y. *Tetrahedron Lett.* **1981**, *22*, 4969–4972; (e) Nakagawa, M.; Taniguchi, M.; Sodeoka, M.; Ito, M.; Yamaguchi, K.; Hino, T. *J. Am. Chem. Soc.* **1983**, *105*, 3709–3710.
3. Bock, M. G.; Dipardo, R. M.; Pitzenberger, S. M.; Homnick, C. F.; Springer, J. P.; Friedinger, R. M. *J. Org. Chem.* **1987**, *52*, 1644–1646.
4. Nakagawa, M.; Ito, M.; Hasegawa, Y.; Akashi, S.; Hino, T. *Tetrahedron Lett.* **1984**, *25*, 3865–3868.
5. (a) Al-Said, N. H.; Al-Qaisi, L. S. *Tetrahedron Lett.* **2006**, *47*, 693–694; (b) He, F.; Foxman, B. M.; Snider, B. B. *J. Am. Chem. Soc.* **1998**, *120*, 6417–6418; (c) He, F.; Snider, B. B. *Synlett* **1997**, 483–484; (d) Marsden, S. P.; Depew, K. M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1994**, *116*, 11143–11144.
6. (a) Liu, J.; Kaselj, M.; Isome, Y.; Chapnick, J.; Zhang, B.; Bi, G.; Yohannes, D.; Yu, L.; Baldino, C. M. *J. Org. Chem.* **2005**, *70*, 10488–10493; (b) Liu, J.-F.; Ye, P.; Zhang, B.; Bi, G.; Sargent, K.; Yu, L.; Yohannes, D.; Baldino, C. M. *J. Org. Chem.* **2005**, *70*, 6339–6345; (c) Xue, S.; Mckenna, J.; Shieh, W.-C.; Repic, O. *J. Org. Chem.* **2004**, *69*, 6474–6477.
7. Wipf, P.; Miller, C. P. *J. Org. Chem.* **1993**, *58*, 3604–3606.
8. (a) Wang, H.; Ganesan, A. *J. Org. Chem.* **1998**, *63*, 2432–2433; (b) He, F.; Snider, B. B. *J. Org. Chem.* **1999**, *64*, 1397–1399; (c) Hart, D. J.; Magomedov, N. *Tetrahedron Lett.* **1999**, *40*, 5429; (d) Mazurkiewicz, R. *Monatsh. Chem.* **1989**, *120*, 973.
9. (a) Kende, A. S.; Fan, J.; Chen, Z. *Org. Lett.* **2003**, *5*, 3205–3208; (b) Hart, D. J.; Magomedov, N. A. *J. Am.*

*Chem. Soc.* **2001**, *123*, 5892–5899; (c) Witt, A.; Bergman, J. *J. Org. Chem.* **2001**, *66*, 2784–2788; (d) Snider, B. B.; Zeng, H. *Org. Lett.* **2000**, *2*, 4103–4106; (e) Wang, H.; Ganesan, A. *J. Org. Chem.* **2000**, *65*, 1022–1030.

10. (a) Mhaske, S. B.; Argade, N. P. *J. Org. Chem.* **2004**, *69*, 4563–4566; (b) Mhaske, S. B.; Argade, N. P. *Tetrahedron* **2004**, *60*, 3417–3420; (c) Mhaske, S. B.; Argade, N. P. *Synthesis* **2002**, 323–325; (d) Mhaske, S. B.; Argade, N. P. *J. Org. Chem.* **2001**, *66*, 9038–9040.
11. Vorbruggen, H. *Accounts Chem. Res.* **1995**, *28*, 509, and references cited therein.
12. Karimi, B.; Golshani, B. *J. Org. Chem.* **2000**, *65*, 7228.