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COMMUNICATION

Synthesis of 1,2,4-triazines and the triazinoisoquinolinedione DEF ring system of noelaquinone†‡§

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The intramolecular Staudinger-aza-Wittig reaction is used for a general synthesis of 1,2,5,6-tetrahydro-1,2,4-triazines, a structural motif reported for the natural product noelaquinone. The DEF moiety of noelaquinone was obtained in 13 steps and 2% overall yield, and the structure of the synthetic product was confirmed by X-ray analysis.

Noelaquinone **1** (Fig. 1) was isolated in 1998 by Paul Scheuer and coworkers from the Indonesian *Xestospongia* sp.[1] The structure assignment of this marine metabolite was mainly based on NMR analyses, and its biological activities have not yet been explored. However, the hexacyclic noelaquinone ring system is closely related to halenaquinone, xestoquinone, and the viridin class of furanosteroids, many of which have shown potent kinase inhibitory effects.[2,3] A distinct feature of noelaquinone is its DEF 3,4-dihydro-2*H*-[1,2,4]triazino[2,3-*b*]isoquinoline-6,11-dione, a heterocycle that has hitherto never been synthesized.

The absence of any information on its biological profile and the presence of a unique heterocyclic ring system make noelaquinone an attractive target for total synthesis. Herein, we report a new method for the formation of fused 1,2,4-triazines and its application to the first preparation of the DEF ring system in **1**.

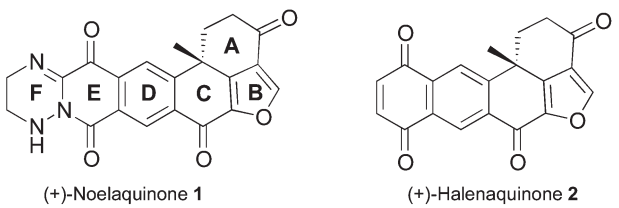
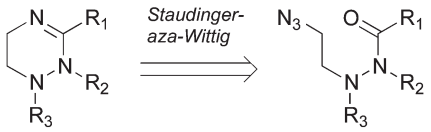
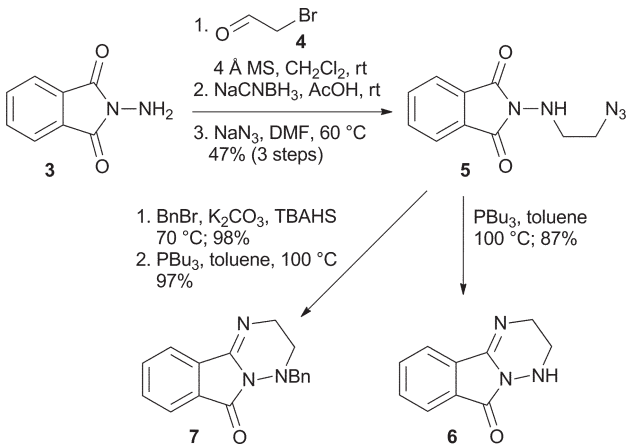


Fig. 1 Polycyclic furans isolated from the marine sponge *Xestospongia*.



Scheme 1 Retrosynthesis of 1,2,5,6-tetrahydro-1,2,4-triazines.



Scheme 2 Preparation of triazino-isoindolones from *N*-amino-phthalimide.

As a key step for the expedient formation of 1,2,4-triazines, we planned to develop a variant of the intramolecular Staudinger-aza-Wittig reaction. This method has proven to be a useful tool in natural products synthesis,[4] and we decided to further explore its application for the ring closure of an azido-hydrazide precursor (Scheme 1).

Due to its ready availability and high chemical reactivity, we first used *N*-aminophthalimide **3** as a model system (Scheme 2). Azide **5** was obtained in three steps and 47% yield from **3** by condensation with α-bromoacetaldehyde **4**[5] in the presence of 4 Å molecular sieves to give the α-bromohydrazone. Since this intermediate was found to be very labile, it was reduced without isolation with $NaCNBH_3$ to give the corresponding bromoethyl derivative, which was converted to alkyl azide **5** with sodium azide in DMF.

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‡ Dedicated to the memory of Prof. Robert E. Ireland.

§ Electronic supplementary information (ESI) available: Synthetic protocols and spectroscopic data. CCDC 868588–868590. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2ob25353d

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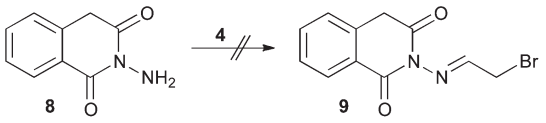
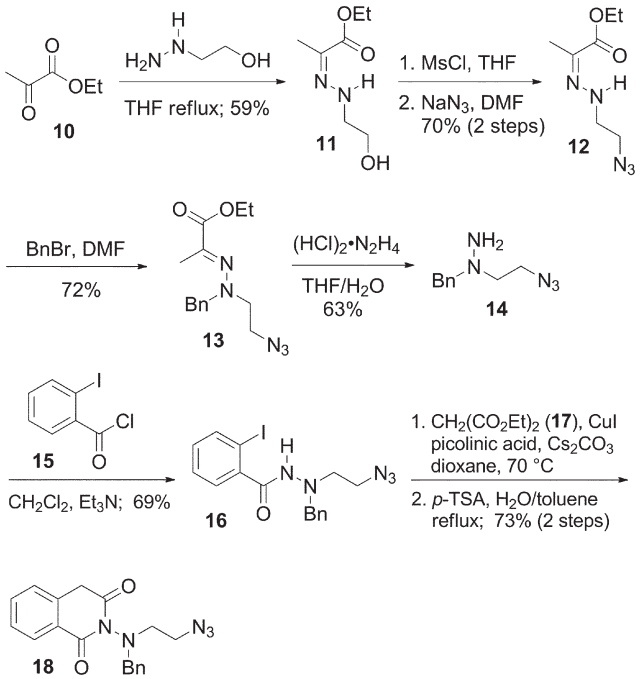
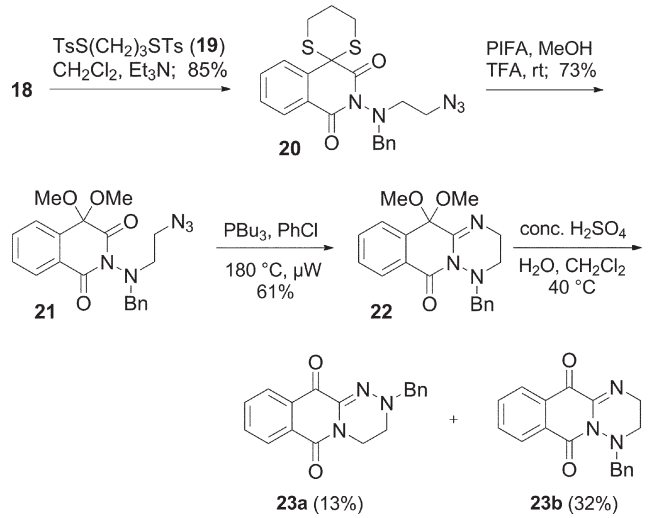


Scheme 3 Failed hydrazone formation.



Scheme 4 Preparation of homophthalimide **18** by a key copper-catalyzed C-arylation.



Scheme 5 Formation of isomeric triazinoisoquinolines under acidic acetal hydrolysis conditions.

When azide **5** was heated in toluene at 100 °C in the presence of 2 equiv of PBu_3, a clean conversion to the desired triazinone **6** occurred. Alternatively, the hydrazide was *N*-protected with benzyl bromide in the presence of tetrabutylammonium hydrogen sulfate (TBAHS), and the phosphine treatment afforded the corresponding triazinone **7** in 97% yield. The *N*-benzylated triazinone **7** was much easier to isolate and purify than the unprotected **6**.

The successful conversion of model azido-hydrazide **5** into triazino[3,2-*a*]isoindolones **6** and **7** encouraged us to explore the preparation of triazino[2,3-*b*]isoquinolines. However, we were unable to isolate the requisite intermediate α-bromohydrazone **9** from hydrazide **8** under typical condensation conditions with aldehyde **4** (Scheme 3). While the hydrazone appeared to form, decomposition during the reaction resulted in the formation of a complex mixture at workup.

After several unsuccessful attempts to add the azide moiety to the homophthalimide ring system, we were able to develop a strategy that installed the cyclic imide on a prefunctionalized hydrazide (Scheme 4). Protection of 2-hydroxyethylhydrazine with ethyl pyruvate **10** gave hydrazone **11** in 59% yield. Mesylation of the alcohol and treatment with NaN_3 led to azide **12**, which was selectively benzylated and then hydrolyzed to give the azido-hydrazine **14**. After acylation of **14** with *o*-iodobenzoylchloride **15**, a C-arylation[6] of diethylmalonate **17** in the presence of 5 mol% of Cu(I)-catalyst, 10 mol% of picolinic acid, and 3 equiv of Cs_2CO_3 in dioxane led to the α-aryl malonate intermediate, which was used crude after workup. The homophthalimide ring was readily obtained by treatment with catalytic *p*-toluenesulfonic acid (*p*-TSA) in aqueous toluene, which promoted a cascade cyclization–decarboxylation to yield **18** in 73% over 2 steps.

In preparation for the introduction of the benzylic ketone function, **18** was converted to thioacetal **20** by treatment with trimethylene dithiotosylate **19** (Scheme 5).[7] Acetal exchange to the dimethyl acetal **21** was accomplished with iodobenzenebis-trifluoroacetate (PIFA) in methanol in the presence of trifluoroacetic acid.[8] The Staudinger-aza-Wittig reaction of **21** proceeded smoothly under microwave irradiation conditions to give the desired triazine **22** in 61% yield, but all attempts to hydrolyze the acetal to unmask the carbonyl group either decomposed the product or provided a 2.5 : 1 mixture of the isomeric triazinoisoquinolines **23a** and **23b** in modest 45% combined yield. The structures of **23a** and **23b** were unambiguously assigned by X-ray crystallographic analysis (Fig. 2).

While the formation of **23b** accomplished our goal to access the DEF ring system of **1**, we were unable to identify acetal hydrolysis conditions avoiding the equilibration of this heterocyclic system to the isomeric 3,4-dihydro-2*H*-[1,2,4]triazino-[4,3-*b*]isoquinoline-6,11-dione **23a**. Furthermore, we were unable to cleave the benzyl protecting group in either **23a** or **23b**.

Accordingly, we modified the synthetic route shown in Schemes 4 and 5 by using the *p*-methoxybenzyl (PMB) protected azido hydrazine **24** (Scheme 6). Acylation of **15**, C-arylation with malonate **17**, and cyclization–decarboxylation proceeded uneventfully to give homophthalate **25**. In two steps, the benzylic methylene group in **25** was converted to the dimethyl acetal and the Staudinger-aza-Wittig reaction provided triazine **26** in high yield. Interestingly, controlled hydrolysis in cold sulfuric acid removed the PMB group in 72% yield without cleavage of the dimethyl acetal. The resulting dimethyl acetal **27**

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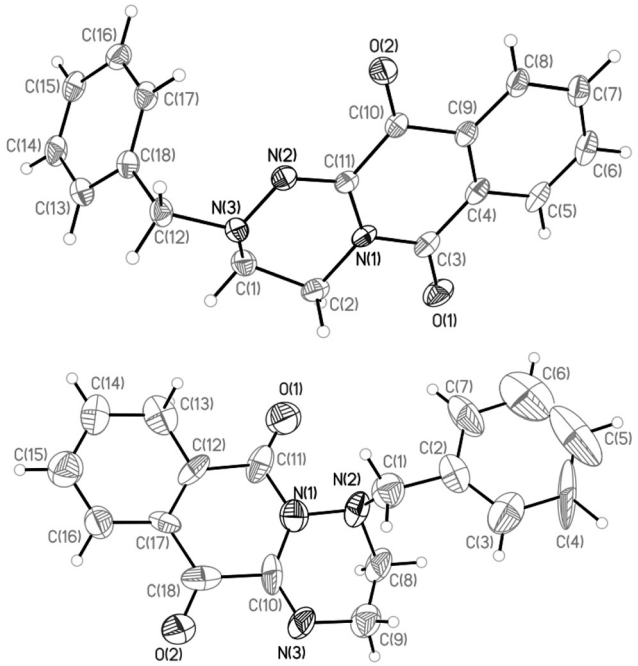
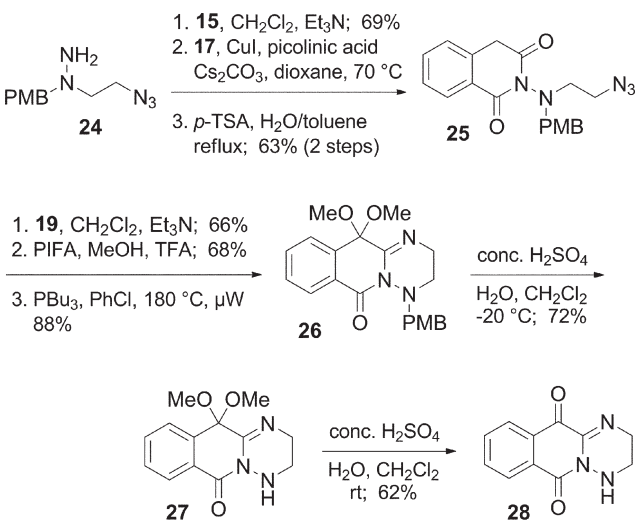


Fig. 2 X-Ray structures of **23a** (top) and **23b** (bottom).



Scheme 6 Preparation of the DEF ring system of noelaquinone from the PMB-protected azido hydrazine **24**.

was subjected to hydrolysis in conc. H_2SO_4 at room temperature to yield the desired unprotected triazino[2,3-*b*]isoquinoline **28** in the absence of any rearrangement products. The difference in the reactivities of **22** and **27** in the acid catalyzed hydrolysis is quite striking. We speculate that the increased solvation of the less lipophilic **27** increases the stability of the intermediate oxocarbenium ion, thus allowing for a quicker acetal cleavage at slightly lower temperature and preventing the triazine isomerization. The structural assignment of **28** was confirmed by X-ray analysis (Fig. 3).

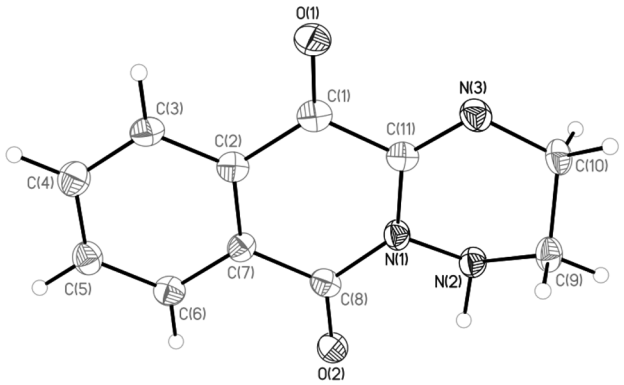


Fig. 3 X-Ray structure of **28**.

Conclusions

We have demonstrated an efficient method to generate azido hydrazines, thus enabling the application of the Staudinger-aza-Wittig reaction of imides as a general method for the preparation of tetrahydro-1,2,4-triazines. For the synthesis of the DEF ring system of noelaquinone, the Cu(I)-catalyzed C-arylation of diethyl malonate was used to access the key intermediate homophthalimides **18** and **25**. The use of the PMB protective group and controlled acidic hydrolysis conditions led to the first preparation of the heterocycle **28**, previously reported for the DEF ring moiety of the natural product noelaquinone. In the course of this synthesis, we also observed the equilibration of triazinoisoquinolines **23a** and **23b** under acidic conditions, most likely *via* an ANRORC[9] mechanism.

Acknowledgements

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Notes and references

1 Y. Zhu, W. Y. Yoshida, M. Kelly-Borges and P. J. Scheuer, *Heterocycles*, 1998, **49**, 355.
2 (*a*) P. Wipf and R. J. Halter, *Org. Biomol. Chem.*, 2005, **3**, 2053; (*b*) B. Wakefield, R. J. Halter and P. Wipf, *Org. Lett.*, 2007, **9**, 3121; (*c*) Y. Lang, F. E. S. Souza, X. Xu, N. J. Taylor, A. Assoud and R. Rodrigo, *J. Org. Chem.*, 2009, **74**, 5429; (*d*) A. D. Findlay, A. Gebert, I. A. Cade and M. G. Banwell, *Aust. J. Chem.*, 2009, **62**, 1173; (*e*) K. M. Muller and B. A. Keay, *Synlett*, 2008, 1236; (*f*) E. H. Sessions and P. A. Jacobi, *Org. Lett.*, 2006, **8**, 4125; (*g*) P. Wipf, D. J. Minion, R. J. Halter, M. I. Berggren, C. B. Ho, G. G. Chiang, L. Kirkpatrick, R. Abraham and G. Powis, *Org. Biomol. Chem.*, 2004, **2**, 1911; (*h*) N. T. Ihle, R. Williams, S. Chow, W. Chew, G. Paine-Murrieta, D. J. Minion, R. J. Halter, P. Wipf, R. Abraham, L. Kirkpatrick and G. Powis, *Mol. Cancer Ther.*, 2004, **3**, 763.
3 (*a*) J. R. Hanson, *Nat. Prod. Rep.*, 1995, **12**, 381; (*b*) A. Longeon, B. R. Copp, M. Roue, J. Dubois, A. Valentin, S. Petek, C. Debitus and M.-L. Bourguet-Kondracki, *Bioorg. Med. Chem.*, 2010, **18**, 6006.
4 (*a*) S. Eguchi, *ARKIVOC*, 2005, **ii**, 98; (*b*) P. H. Lambert, M. Vaultier and R. Carrie, *J. Org. Chem.*, 1985, **50**, 5352; (*c*) H. Takeuchi and S. Eguchi, *Tetrahedron Lett.*, 1989, **30**, 3313; (*d*) J. Chen and C. J. Forsyth, *Org. Lett.*, 2003, **5**, 1281–1283; (*e*) S. Bräse, C. Gil, K. Knepper and V. Zimmermann, *Angew. Chem., Int. Ed.*, 2005, **44**,

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5188; (*f*) Z.-B. Chen, D. Hong and Y.-G. Wang, *J. Org. Chem.*, 2009, **74**, 903; (*g*) A. Tarraga, P. Molina, D. Curiel and M. D. Velasco, *Tetrahedron*, 2001, **57**, 6765; (*h*) R. Brossmer and H. Mack, *Tetrahedron Lett.*, 1981, **22**, 933.
5 M. Jachak, M. Mittelbach and H. Junek, *Org. Prep. Proced. Int.*, 1993, **25**, 469.
6 (*a*) X. Xie, G. Cai and D. Ma, *Org. Lett.*, 2005, **7**, 4693; (*b*) S. F. Yip, H. Y. Cheung, Z. Zhou and F. Y. Kwong, *Org. Lett.*, 2007, **9**, 3469.
7 R. B. Woodward, I. J. Pachter and M. K. Scheinbaum, *Org. Synth.*, 1974, **54**, 39.
8 G. Stork and K. Zhao, *Tetrahedron Lett.*, 1989, **30**, 287.
9 H. C. van der Plas, *Adv. Heterocycl. Chem.*, 1999, **74**, 1.

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