Tetrahedron Letters 51 (2010) 1262–1264

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Expedient access to fused quinoxalines via Dess–Martin periodinane-mediated cyclization of unsymmetrical phenylenediamide derivatives

Cristian Dobrotă [a,*], Jonathan Graeupner [b], Ioana Dumitru [a], Mihaela Matache [a], Codruta C. Paraschivescu [a]

[a] University of Bucharest, Department of Chemistry, Şoseaua Panduri, 90-92, Sector 5, 050657 Bucharest, Romania
[b] Technical University of Munich, Chemistry Dept, Lichtenbergstr, 4, 85747 Garching, Germany

ARTICLE INFO

Article history:
Received 21 October 2009
Accepted 17 November 2009
Available online 22 November 2009

ABSTRACT

One-pot cyclization of various 2-*N*-amido-homoallylanilides mediated by 4 equiv of Dess–Martin periodinane produced pyrrolo[1,2-*a*]quinoxalines (11 examples, up to 93% yield).

The enormous potential of polyvalent iodine compounds as reagents for a wide variety of oxidative processes has been proven by the large number of research papers published on this topic in recent years.[1] Among them, the Dess–Martin periodinane[2] **1** (DMP–1,1,1-triacetoxy-1,2-benzoiodoxol-3-one) and its synthetic precursor IBX **2** (1-hydroxy-1-oxo-1,2-benzoiodoxol-3-one) play a key role, mainly due to their ability to effectively oxidize alcohols to carbonyls under mild conditions. Moreover, various classes of heterocycles have been lately reported as a result of the oxidative transformations mediated by DMP and IBX.[3]

In this context, the formation of *N*-aryl pyrollidones **3** and related fused heterocycles, such as pyrrolo[1,2-*a*]benzoxazines **4** is of particular interest (Fig. 1). This cascade oxidative cyclization of unsaturated anilides in the presence of DMP or IBX (Scheme 1) was discovered more than a decade ago by Nicolaou and his coworkers during the synthesis of CP molecules.[4]

Exploring this new reaction, they reported related processes for a large variety of anilides, urethanes, or ureas, proving the utility of the complex structures thus obtained for the preparation of aminoalcohols or aminosugars.[5] We dare to name this transformation the Nicolaou reaction. Soon thereafter, bis(trifluoroacetoxy)-iodobenzene (BTI) was discovered to mediate similar transformations.[6]

Mechanistic studies proved that the cascade process occurs via an *ortho*-aza quinone intermediate, which leads to the final product by a hetero-Diels cycloaddition. Moreover, it has been demonstrated that vicinal groups may play a role in the outcome of the Nicolaou reaction.[4]

We report herein an extension of this versatile reaction: the one-pot preparation of fused quinoxaline derivatives starting from various phenylenediamides bearing at least one homoallylic amide moiety. The quinoxalines are interesting frameworks for drug development, mainly due to their structural similarity to benzodiazepines. However, despite the wide range of biological activities exhibited by functionalized quinoxalines,[7] their preparation was far less studied compared to the benzodiazepines.

To test the behavior of a homoallylic phenylenediamide in the conditions of the Nicolaou reaction, we prepared a model substrate that has two susceptible moieties able to undergo the oxidative cyclization process, namely bis(*N*,*N*′-dipentenoyl)-1,2-phenylenediamine **5a**. Thus, we submitted **5a** to the action of an excess of DMP in the conditions reported previously.[4] Following the progress of the reaction, we observed the formation of a single product that we identified to be the hexahydropyrrolo[1,2-*a*]quinoxaline **6a** (36% yield, entry 1 in Table 1). This particular class of heterocycles has been obtained before through the cyclization of quinoxalinylpropanoic acids.[8]

The formation of this type of products (i.e., quinoxalines **6**) can be explained following the general mechanistic pathway proposed by Nicolaou.[4] In this particular case, after the initial ligand exchange between DMP **1** and anilide **5**, the vicinal amide moiety probably plays an active part in the formation of the key heterodiene system, which by an intramolecular [4+2] cycloaddition leads to the final product (Scheme 1).

Stimulated by this result, we decided to find the optimal conditions and reagents for this transformation. Since in our case the addition of water did not affect the yield,[4] we performed all cyclization reactions in dichloromethane, without any other additives.

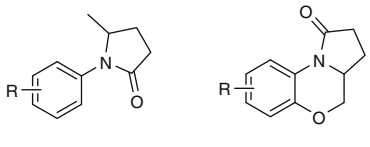
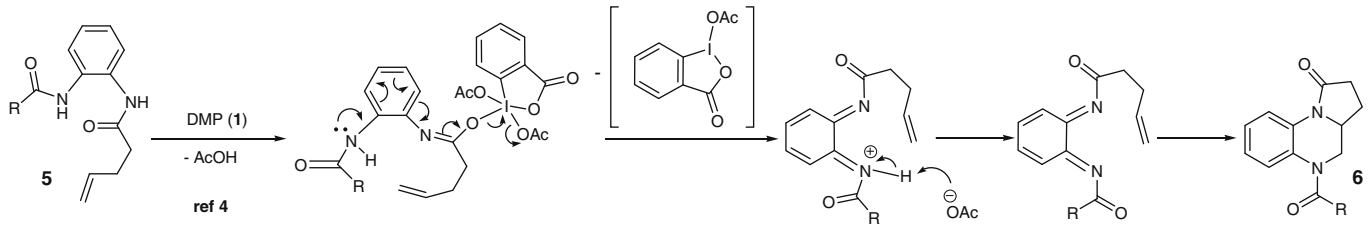


Figure 1. Heterocyclic scaffolds obtained from homoallylic benzamides.

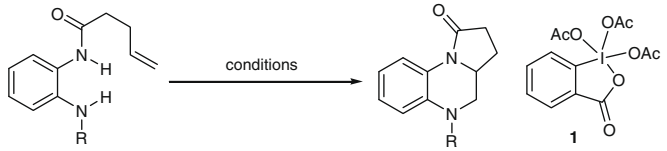
* Corresponding author.
E-mail address: cdobrota@gw-chimie.math.unibuc.ro (C. Dobrotă).

0040-4039/$ - see front matter © 2010 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2009.11.080



Scheme 1. Plausible mechanism for the formation of quinoxaline derivatives in the oxidative cyclization of unsymmetrical homoallylic phenylenediamides.

Table 1
Oxidative cyclization of **5a–d** to pyrrolo[1,2-*a*]quinoxalines[10] **6a–d** in presence of DMP **1**



Entry	Substrate	R	Conditions[a]	Yield[c] (%)
1	**5a**	CH_2=CH–$(CH_2)_2$–CO–	4 equiv of **1**	36
2	**5a**	CH_2=CH–$(CH_2)_2$–CO–	4 equiv of **1**	37[d]
3	**5a**	CH_2=CH–$(CH_2)_2$–CO–	6 equiv of **1**	40
4	**5a**	CH_2=CH–$(CH_2)_2$–CO–	4 equiv BTI[b]	—[e]
5	**5a**	CH_2=CH–$(CH_2)_2$–CO–	4 equiv PIDA	—[e]
6	**5b**	Ph-CO–	4 equiv of **1**	66
7	**5c**	4-MeO–C_6H_4–CO–	4 equiv of **1**	81
8	**5d**	Ph	4 equiv of **1**	—[e]

[a] 20 h under argon at rt in dry dichloromethane.
[b] 6 h in the same conditions.
[c] Isolated yields.
[d] 2 equiv of water was added.
[e] Decomposition of the substrate under the reaction conditions.

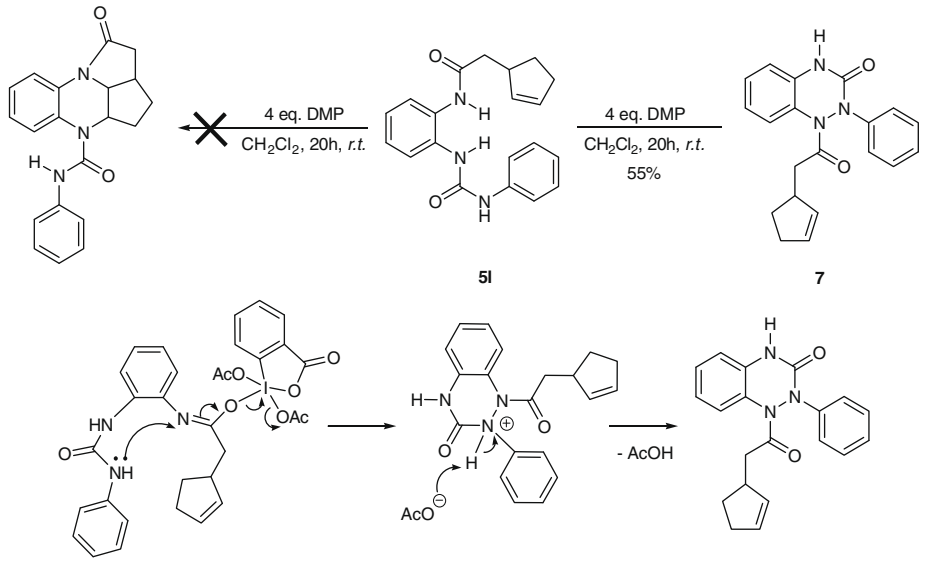
A ratio of 4:1 DMP/substrate was found to be optimal with respect to the cyclization product yield (entries 2–5 in Table 1). Moreover, use of trivalent iodine-containing reagents (BTI or PIDA—iodobenzenediacetate) in the same reaction conditions led to substrate decomposition.

The benzoyl derivative **5b** led to the desired product **6b** in a higher yield of 66% (Table 1, entry 6), proving the superiority of arylamides as vicinal groups in the substrates. A further increase of the electronic density on the aryl ring in the vicinal amide (i.e., use of the 4-methoxyphenyl-carboxamide, PMP–CO–) resulted in the formation of the tricyclic compound **6c** in 81% (Table 1, entry 7), while the attempt to employ a secondary diarylamine (substrate **5d**) in the process failed (Table 1, entry 8).

Endocyclic olefins are known to be better substrates for the Nicolaou reaction compared to their acyclic counterparts.[4] Therefore, we synthesized the series of *ortho*-substituted methylcyclopent-2-enoylbenzamides **5e–l** bearing various substituents on the nitrogen atom and submitted it to the action of **4** equiv of DMP (Table 2). This scoping ensures not only retrieval of the best conditions for the cyclization process, but would also provide the desirable methodological flexibility in organic synthesis.[9] Satisfactorily, all the substrates tested were completely converted in the presence of DMP **1** and they all yielded the desired tetracyclic structures **6e–k** as major products, with one notable exception, which led to an unexpected product (substrate **5l**, vide infra, Scheme 2).

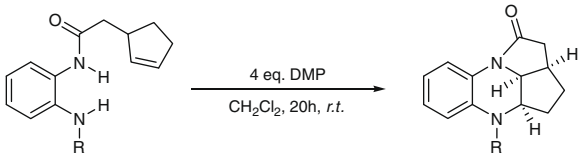
This series of fused quinoxalines is structurally similar to the benzoxazine derivatives prepared in almost identical conditions by the group of Nicolaou.[4] Indeed, the proton NMR spectra of quinoxalines **6a–k** are very similar to those of the corresponding reported benzoxazines. Based on this fact as well as bidimensional NMR correlation experiments, we also propose the *syn* junction for all the cycles of the fused quinoxaline derivatives obtained by cascade cyclizations in the presence of DMP.[10]

Interestingly, the attempt to use a substrate having a urea moiety (i.e., **5l**) led to the formation of an unexpected product.



Scheme 2. Preparation of benzotriazine derivative **7** by oxidative cyclization of urea-substituted benzamide **5l**.

Table 2
Oxidative cyclization of **5e**–**k** to pyrrolo[1,2-*a*]quinoxalines[10] **6e**–**k** in the presence of DMP **1**



5e-k **6e-k**

Entry	Substrate	R	Yield[a] (%)
1	**5e**	2-(Cyclopent-2-enyl)acetyl	60
2	**5f**	Ph-CO–	78
3	**5g**	4-MeO–C_6H_4–CO–	93
4	**5h**	4-O_2N–C_6H_4–CO–	63
5	**5i**	4-Me-C_6H_4–SO_2–	75
6	**5j**	EtO-CO–	71
7	**5k**	$(EtO)_2PO$–	49

[a] Isolated yields.

Although the progress of the reaction was similar, with complete conversion of the substrate toward a major compound, the polarity of the product isolated was much lower compared to that of the other fused tetracyclic quinoxalines. This product was identified as the benzo[*e*][1,2,4]triazine derivative **7** (Scheme 2). Its formation may be explained by the attack of the far-sided nitrogen of the urea moiety on the imidoester, thus closing the six-membered triazine ring.

In conclusion, we described an original and effective access to fused quinoxaline derivatives, via a cascade cyclization process mediated by an excess of Dess–Martin periodinane. Further investigation of this versatile process is currently under study and will be reported in due course.

Supplementary data

Supplementary data (detailed experimental procedures for the preparation of substrates **5a–l** and products **6a–k** and **7**, as well as copies of NMR spectra of all the compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.11.080.

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10. See Supplementary data for details.