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Hypervalent iodine-mediated oxidative cyclisation of *p*-hydroxy acetanilides to 1,2-dispirodienones†

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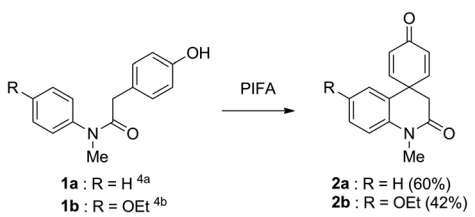
Laurent Chabaud,* Tatiana Hromjakova, Matt Rambla, Pascal Retailleau and Catherine Guillou*

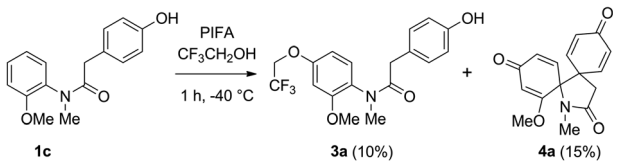
1,2-Dispirodienones were synthesized by hypervalent iodine-mediated phenolic oxidation of *p*-hydroxy acetanilides. The reaction is compatible with several substituted anilides and affords a new class of 1,2-dispirodienones that are remarkably stable under thermal or acidic conditions.

Since the last few decades, hypervalent iodine reagents, such as phenyliodine(III) bis(trifluoroacetate) (PIFA) and phenyliodine(III) diacetate (PIDA), have gained importance in the oxidative phenolic coupling reactions.[1] These non-toxic, safe and easy handling reagents have found many applications in the biomimetic synthesis of natural alkaloids. Intramolecular phenol-coupling reaction using hypervalent iodine proved to be a powerful tool for the formation of spirocyclohexadienones that are key intermediates in the total synthesis of Amaryllidaceae[2] and Discorhabdin alkaloids.[3] Recently, this methodology has been applied to the synthesis of spirodienone lactams such as **2a–b** (Scheme 1).[4]

In a project aimed at the synthesis of natural products, we planned to synthesize a spirodienone lactam by oxidation of *ortho* methoxy anilide **1c** (Scheme 2). Surprisingly, treatment of **1c** with PIFA in trifluoroethanol (TFE) at −40 °C resulted in extensive substrate polymerization, as well as the formation of phenol **3a** incorporating a molecule of solvent, and the original 1,2-dispirodienone **4a** in low yields (Scheme 2).



Scheme 1 Oxidation of phenol acetanilides **1a–1b**.



Scheme 2 Oxidation of **1c** with PIFA.

1,2-Dispirodienones are unusual motifs that have received very little attention. The synthesis of these compounds usually relies on the intramolecular biradical coupling of bis(2,6-di-*tert*-butylphenol) in the presence of PbO_2, $K_3Fe(CN)_6$ or DDQ.[5] Only one synthesis of 1,2-dispirodienone lacking the *tert*-butyl groups has been reported so far, but this compound rapidly decomposed in the solid state at room temperature.[5g]

Intrigued by the reactivity of acetanilide **1c** and the structure of the 1,2-dispirodienone **4a**, we studied the synthesis of this new class of 1,2-dispirodienones using hypervalent iodine reagents. Having isolated **3a** and **4a** in the same reaction mixture, we speculated that 1,2-dispirodienone **4a** could be the result of the oxidation of phenol **3a** with concomitant loss of the trifluoroethyl group. To test this hypothesis, phenol **3a** was oxidized with PIFA and exclusively afforded the 1,2-dispirodienone **4a** in 75% yield (Table 1, entry 1). We found that the 2,4-dimethoxy anilide **3a′** also gave the same product under these conditions (entry 2). The reaction is tolerant with *O*-benzyl or *N*-benzyl protected anilide **3b** and **3c** respectively (entries 3–4). The amide **3d** bearing an electron-withdrawing protecting group (Boc) also reacted well, but gave a mixture of the 1,2-dispirodienone **4d** and the cyclic carbamate **5** resulting from the attack of the *tert*-butylcarbamate group (entry 5). The reaction is also compatible with anilide **3e** bearing a chlorine atom at the 5-position (entry 6). More electron-rich trimethoxy anilides **3f–3h** were also examined in this reaction (entries 7–9). As expected, compounds **3f** and **3g** gave the corresponding 1,2-dispirodienones **4f** and **4g** respectively. The course of the reaction was modified when the 2,3,4-trimethoxy aniline **3h** was used, exclusively giving

Centre de Recherche de Gif, Institut de Chimie des Substances Naturelles, CNRS, LabEx LERMIT, 1 avenue de la Terrasse, 91198, Gif-sur-Yvette, France. E-mail: catherine.guillou@cnrs.fr, laurent.chabaud@cnrs.fr; Fax: +33 (0)1 69 07 72 47

† Electronic supplementary information (ESI) available: Detailed experimental procedures and spectroscopic data. CCDC 828700. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3cc47171c

Table 1 Substrate scope of the oxidation[a]

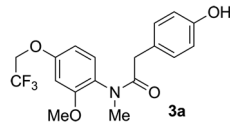
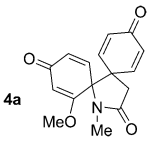
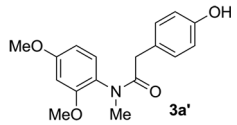
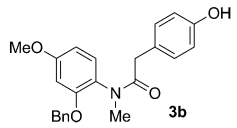
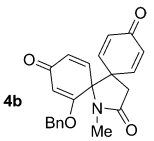
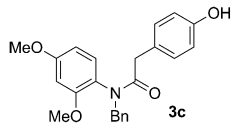
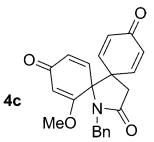
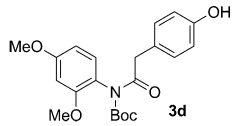
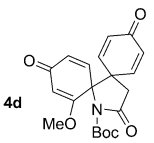
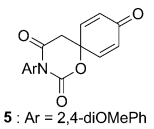
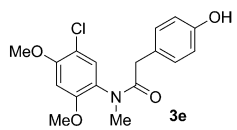
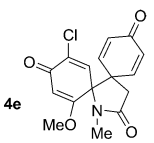
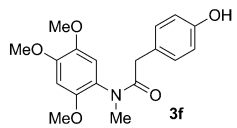
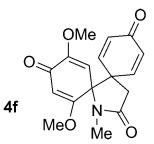
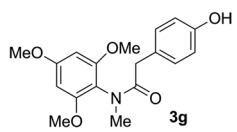
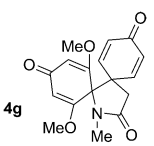
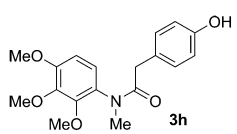
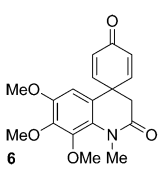
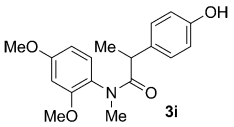
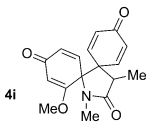
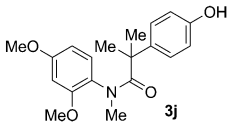
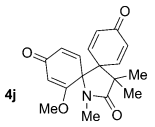
Entry	Substrate	Product	Yield[b] (%)
1	 **3a**	 **4a**	75
2	 **3a'**		80
3	 **3b**	 **4b**	82
4	 **3c**	 **4c**	64
5	 **3d**	 **4d**	40
		 **5** : Ar = 2,4-diOMePh	28
6	 **3e**	 **4e**	60
7	 **3f**	 **4f**	69
8	 **3g**	 **4g**	77
9	 **3h**	 **6**	61

Table 1 (*continued*)

Entry	Substrate	Product	Yield[b] (%)
10	 **3i**	 **4i**	86[c]
11	 **3j**	 **4j**	39

[a] Reaction conditions: substrate 1 eq., PIFA 1.2 eq., in TFE (0.033 M) at −40 °C for 1 h. [b] Isolated yield after purification through silica gel. [c] d.r. = 52/48.

the spirodienone **6** (entry 9). The phenol **3i** with a methyl group at the α position of the carbonyl gave the spirocycle **4i** in good yield, but with no diastereoselectivity (entry 10).

Interestingly, the *gem*-dimethyl substituted anilide **3j** provided the sterically congested dispirodienone **4j** having three contiguous quaternary carbon. Compound **4j** was the only product observed by ^{1}H NMR of the crude mixture, and the modest isolated yield might be due to its instability on silica gel.

The X-ray structure[6] of the 1,2-dispirodienone **4a** displays some common structural features with the related *tert*-butyl-substituted 1,2-dispirodienones prepared by diphenol oxidation (Fig. 1).[5a,c,f] The plane of the cyclohexadienones is nearly perpendicular to the pyrrolidinone ring that adopts a slightly distorted envelope conformation. Another characteristic is the length of the endocyclic C(4)–C(10) bond which is longer (1.615 Å) than a standard Csp^3–Csp^3 bond (1.54 Å).

Despite the high C(4)–C(10) bond length, no indication of cleavage was observed upon heating **4a** at 100 °C overnight in toluene-d_8 or DMSO-d_6. The 1,2-dispirodienone **4a** also remained intact when treated with trifluoroacetic acid in dichloromethane overnight. However, stirring of **4a** with hydrochloric acid (2 N) in a THF–H_2O mixture for two days afforded diphenol **8** in 65% yield (Scheme 3).

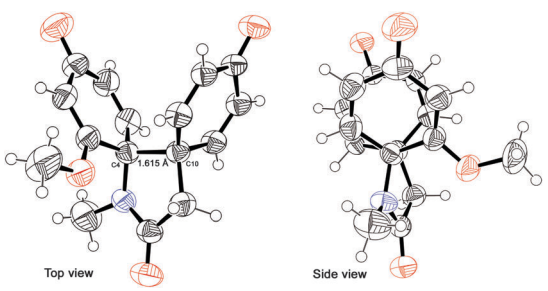
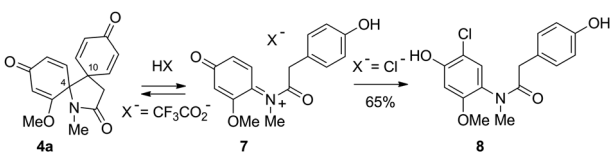
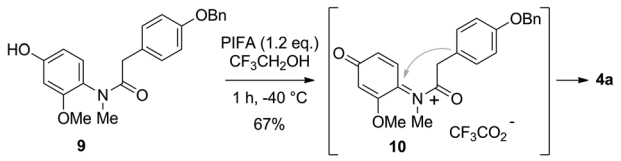


Fig. 1 Ortep representation of **4a**.



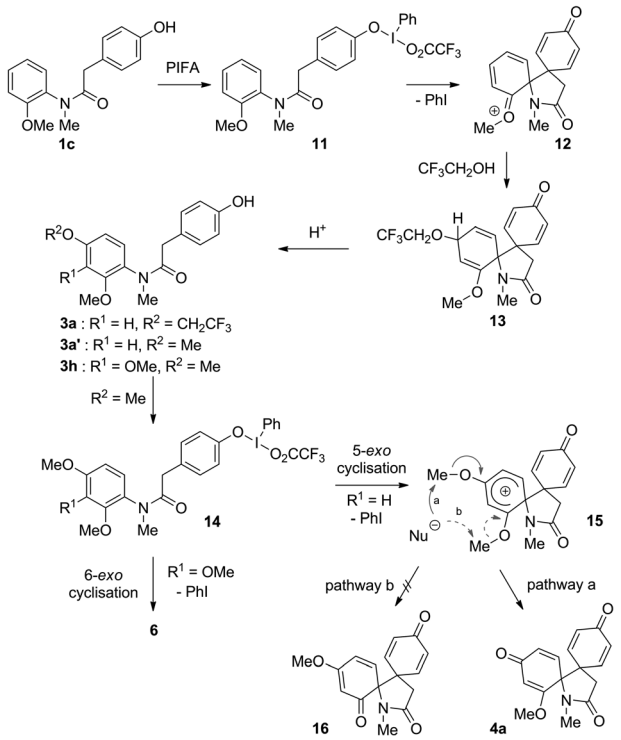
Scheme 3 Stability of the dispirodienone **4a** under acidic conditions.



Scheme 4 Oxidation of phenol **9**.

The apparent thermal and acidic stability (with TFA) as well as the formation of **8** (with aqueous HCl) suggest that the cleavage of the endocyclic C(4)–C(10) bond of **4a** could occur to afford the iminium **7** (or the phenolate under thermal conditions). In the absence of a nucleophile (thermal conditions) or in the presence of a weak nucleophile ($X^- = CF_3CO_2^-$), this step might be reversible. However, with aqueous HCl, the chlorine anion is nucleophilic enough to add to the iminium **7** leading to the rearomatized product **8**. Although we did not have any evidence of a possible equilibrium between **4a** and **7**, we showed in a separate experiment that the oxidation of **9** produced the 1,2-dispirodienone **4a** in 67% yield (Scheme 4). We presumed that oxidation of **9** with PIFA should give the iminium **10**, with a structure similar to **7**, that could cyclize into 1,2-dispirodienone **4a**. This result confirms the feasibility of an intramolecular *para*-alkylation of the phenol ring on the iminium **10** (or **7**) to produce **4a**.

A possible mechanism of the oxidation is depicted in Scheme 5. Initial ligand exchange of **1c** with PIFA would give intermediate **11** that could cyclise into spirocycle **12**. Addition of a molecule of solvent, then aromatisation of **13** would furnish phenol **3a** incorporating a trifluoroethyloxy group in the *para*-position of the nitrogen atom. Oxidation of the 2,4-dialkoxy acetanilides also began by a ligand exchange to form **14**. This intermediate can then evolve through two different pathways depending on the substitution on the aromatic ring. For anilide **3h** (R^1 = OMe), a 6-*exo* cyclisation occurs giving the spirodienone **6**. However, with **3a′** (R^1 = H) and the other substrates (**3a–3g**, **3i–3j**), the nucleophilic attack of the electron rich aromatic ring proceeds through a 5-*exo* cyclisation to afford intermediate **15**.



Scheme 5 Proposed mechanism.

The methyl group at the *para*-position of the nitrogen atom (pathway a) is then removed *via* nucleophilic displacement ($Nu^- = CF_3CO_2^-$ or/and solvent) to give the 1,2-dispirodienone **4a**. It is worth mentioning that the formation of the 1,2-dispirodienone **16** has never been observed (pathway b).

In summary, we have discovered a new reaction pathway in the hypervalent iodine-promoted oxidative cyclisation of *para*-hydroxy acetanilides. The oxidation can be applied to various substituted substrates to afford a new class of 1,2-dispirodienone lactams. To our knowledge this is the first example of synthesis of 1,2-dispirodienones using hypervalent iodine reagents. In contrast to the known 1,2-dispirodienones, these compounds are remarkably stable at room temperature as well as upon heating or under acidic conditions. Further studies are in progress to explore the synthetic potential and the biological properties of these original 1,2-dispirodienones.

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Notes and references

1 For selected recent reviews, see: (*a*) V. V. Zhdankin, *ARKIVOC*, 2009, 1; (*b*) T. Dohi and Y. Kita, *Chem. Commun.*, 2009, 2073; (*c*) L. Pouységu, D. Deffieux and S. Quideau, *Tetrahedron*, 2010, **66**, 2235–2261; (*d*) L. F. Silva and B. Olofsson, *Nat. Prod. Rep.*, 2011, **28**, 1722; (*e*) Q. Ding, Y. Ye and R. Fan, *Synthesis*, 2013, 1.

2 For selected examples: (*a*) J. D. White, W. K. M. Chong and K. Thirring, *J. Org. Chem.*, 1983, **48**, 2300; (*b*) Y. Kita, M. Arisawa, M. Gyoten, M. Nakajima, R. Hamada, H. Tohma and T. Takada, *J. Org. Chem.*, 1998, **63**, 6625; (*c*) I. R. Baxendale, S. V. Ley and C. Piutti, *Angew. Chem., Int. Ed.*, 2002, **41**, 2194; (*d*) S. Kodama, Y. Hamashima, K. Nishide and M. Node, *Angew. Chem., Int. Ed.*, 2004, **43**, 2659; (*e*) H. E. Pelish, N. J. Westwood, Y. Feng, T. Kirchhausen and M. D. Shair, *J. Am. Chem. Soc.*, 2001, **123**, 6740; (*f*) T. Dohi, Y. Minamitsuji, A. Maruyama, S. Hirose and Y. Kita, *Org. Lett.*, 2008, **10**, 3559.

3 For selected examples: (*a*) Y. Kita, H. Tohma, M. Inagaki, K. Hatanaka and T. Yakura, *J. Am. Chem. Soc.*, 1992, **114**, 2175; (*b*) H. Tohma, Y. Harayama, M. Hashizume, M. Iwata, M. Egi and Y. Kita, *Angew. Chem., Int. Ed.*, 2002, **41**, 348; (*c*) Y. Wada, K. Otani, N. Endo, Y. Harayama, D. Kamimura, M. Yoshida, H. Fujioka and Y. Kita, *Org. Lett.*, 2009, **11**, 4048.

4 (*a*) L. Moisan, M. Wagner, S. Comesse and E. Doris, *Tetrahedron Lett.*, 2006, **47**, 9093; (*b*) Z. Yu, X. Ju, J. Wang and W. Yu, *Synthesis*, 2011, 860.

5 (*a*) K. Nakatuji, M. Oda, M. Kozaki, Y. Morimoto and K. Okada, *Chem. Lett.*, 1998, 845; (*b*) H. Kurata, S. Kim, K. Matsumoto, T. Kawase and M. Oda, *Chem. Lett.*, 2007, 386; (*c*) H. Kurata, S. Kim, T. Fujimoto, K. Matsumoto, T. Kawase and T. Kudo, *Org. Lett.*, 2008, **10**, 3837; (*d*) E. A. Chandross and R. Kreilick, *J. Am. Chem. Soc.*, 1963, **85**, 2530; (*e*) E. A. Chandross and R. Kreilick, *J. Am. Chem. Soc.*, 1964, **86**, 117; (*f*) V. I. Minkin, E. P. Ivachnenko, A. I. Shif, L. P. Olekhnovitch, O. E. Kompan, A. I. Yanovskii and Y. T. Struchkov, *J. Chem. Soc., Chem. Commun.*, 1988, 990; (*g*) M. N. Afzal, A. D. Allbutt, A. Jordaan and G. W. Kirby, *Chem. Commun.*, 1969, 996.

6 CCDC 828700 (**4a**).

