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A Convenient Approach to Fused Indeno-1,4-diazepinones through Hypervalent Iodine Chemistry

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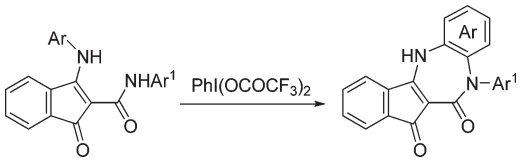

Indenocarboxamides, resulting from the sequential addition of two arylamine equivalents to indanedione ketene dimer, are oxidized by [bis(trifluoroacetoxy)iodobenzene] to fused indeno-1,4-diazepinones in yields depending on the substituents on both aromatic rings. A plausible reaction pathway explaining the formation of the title compounds, as well as the formation of the two other minor products of the reaction, through a common intermediate, is suggested.

Introduction

The chemistry of organic polyvalent iodine compounds has witnessed a great expansion during the last decades, an expansion which continues at an increasing pace. The availability of iodine III and iodine IV compounds and the development of new reagents, along with their selectivity under a variety of conditions, their tolerance to different functional groups, and their low toxicity and ease of handling, made these compounds valuable tools in organic synthesis. As a result of this expansion, a number of books[1] and numerous reviews[2] on the subject have been published.

The majority of hypervalent iodine compounds exhibit oxidative properties, but those that have found widespread application as oxidizing agents are [bis(acyloxy)iodo]arenes (BAIs), $ArI(OCOR)_2$. Among them, [bis(acetoxy)iodo]benzene, $PhI(OAc)_2$, and [bis(trifluoroacetoxy)iodo]benzene, $PhI(OCOCF_3)_2$, are the most representative examples.[2v] In recent publications, the latter is named as phenyliodine(III) bis(trifluoroacetate) and is usually referred by the acronym PIFA.

BAIs' reactivity resembles that of heavy metal reagents. They can oxidize chemoselectively a wide range of functionalities such as alcohols, amines, sulfides, and carbonyl compounds among others, and they are commonly used as effective reagents in various cationic rearrangements and fragmentations. BAIs can serve as excellent oxidants in the degradation of aliphatic and aromatic carboxamides. They have been used for the conversion of amides to alkyl carbamates in alcohol solvents, as well as for the facile oxidative rearrangement of primary aliphatic amides directly to the corresponding amines under extremely mild conditions.[3]

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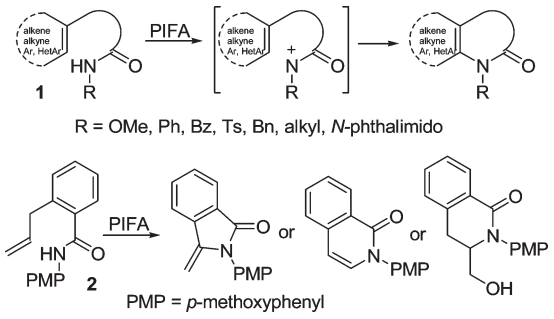
SCHEME 1. General PIFA-Mediated Intramolecular Amidation Process

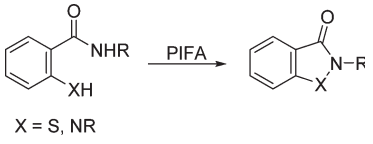


The mechanism of this reaction, an acidic Hofmann rearrangement, has been extensively studied.[3c] An application of this rearrangement in peptide chemistry is the formation of *gem*-aminoamides from *N*-protected amides of natural amino acids[4] and oligopeptides.[5] More recent examples include the oxidative rearrangement of anthranilamides or salicylamides to the respective 2-benzimidazolones or 2-benzoxazolones mediated by $PhI(OAc)_2-KOH/MeOH$.[6]

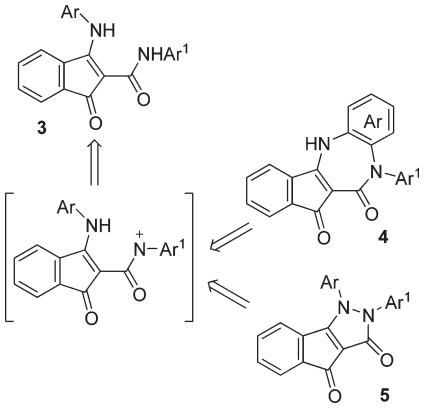
BAIs have also been widely used in several cationic cyclizations. Tellitu and co-workers have developed approaches to the synthesis of nitrogen-containing five-, six-, and seven-membered heterocycles using properly substituted amides as synthetic precursors via PIFA-mediated intramolecular amidation reactions. The oxidation of the amide group by the hypervalent iodine reagent proceeds through the generation of an acylnitrenium intermediate that can react intramolecularly with a nucleophilic moiety properly attached to the substrate. The application of this approach on alkylamides **1** or benzamides **2** bearing alkenyl,[7] alkynyl,[8] aryl,[9,10] or heteroaryl[10] substituents, as well as on properly substituted anilides,[11] led to the synthesis of a plethora of heterocycles through C−N bond formation (Scheme 1).

The same methodology has been successfully applied on 2-mercaptobenzamides[12] and anthranilamides[13] leading to the synthesis of benzisothiazol-3-ones and indazol-3-ones

SCHEME 2. PIFA-Mediated Cyclisation of Mercaptobenzamides and Anthranilamides



SCHEME 3. Retrosynthetic Analysis for Fused Indenodiazepinones and Indenopyrazolinones



through intramolecular trapping of the *N*-acylnitrenium intermediates by the thiol and the amine functionality and formation of N−S and N−N bonds, respectively (Scheme 2).

In the frame of our ongoing interest in the chemistry of hypervalent iodine compounds[14] and the chemistry of aryliodonium ylides of hydroxyquinones more specifically,[15] we reported the synthesis of indenocarboxamides **3** starting from the phenyliodonium ylide of lawsone **10**.[16] The coexistence of the amide together with the arylamino group renders these molecules suitable substrates for oxidation with hypervalent iodine reagents. Having in mind the previously reported methodology, in which the key steps in the oxidation of alkyl amides or benzamides with PIFA are the generation of an *N*-acylnitrenium ion and its subsequent intramolecular trapping by an existing nucleophile, we decided to explore the feasibility of this strategy in the synthesis of the fused indenodiazepinones **4** and/or indenopyrazolinones **5** through a BAI-promoted intramolecular amidation process. A possible retro-synthetic pathway is depicted in Scheme 3.

Pyrazolinones and especially diazepinones constitute important classes of compounds. Pyrazolinones and their fused analogues have found considerable utility as pharmaceutical agents, synthetic scaffolds in combinatorial and medicinal chemistry, photographic couplers, chelating agents, and agrochemical products.[17] Benzodiazepine derivatives exhibit widespread biological activities and consist one of the most important classes of bioavailable therapeutic agents. In addition to their well-known anxiolytic, anticonvulsant, sedative, antihypnotic and muscle-relaxant activities found in therapeutics, benzodiazepines also act as selective cholecystokinin

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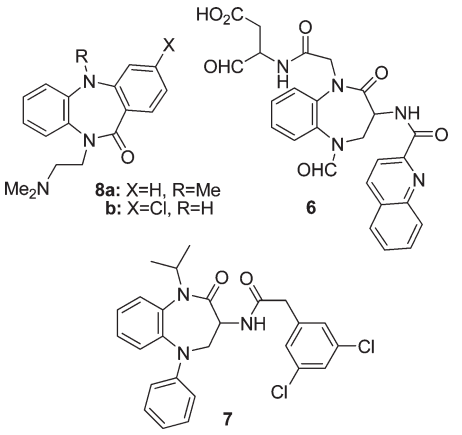


FIGURE 1. Representative examples of 1,5-benzodiazepin-2-ones.

(CCK) receptor subtype A or B antagonists, platelet activating factor antagonists, human immunodeficiency virus (HIV) transactivator Tat antagonists, and enzyme inhibitors.[10b] Due to their capability of binding to multiple receptors with high affinity, benzodiazepines were the class of compounds to which the term "privileged structure" was first applied by Evans et al. in 1988.[18]

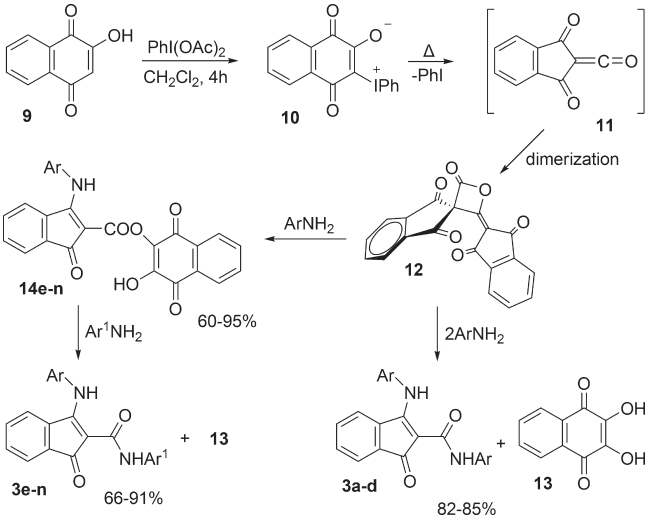
In particular, molecules containing the 1,5-benzodiazepin-2-one as well as the dibenzo[*b*,*e*][1,4]diazepin-11-one scaffold exhibit a wide range of biological properties acting among others as antinflammatories, antitumor agents, and anticonvulsivants.[18,19] Representative examples are the interleukin-1β converting enzyme (ICE) inhibitor **6**, the delayed rectifier potassium current blocker (I_K) **7**, the antidepressant dibenzepine **8a**, and the antihistaminic tarpane **8b** (Figure 1). Containing the 1,5-benzodiazepin-2-one core and a fused indenone nucleus, the potentially accessible diazepinones **4** could be considered as promising biologically active compounds.

Results and Discussion

Indenocarboxamide **3b** and the known compounds **3a**,**c**,**d** were easily prepared from 2-hydroxy-1,4-naphthoquinone (lawsone, **9**) according to a previously reported method.[16] Oxidative treatment of the hydroxyquinone **9** with PhI(OAc)$_2$ affords phenyliodonium ylide **10**, which is thermally converted in refluxing dry CH_2Cl_2 to oxetanone **12** quantitatively (Scheme 4). Oxetanone **12** is the dimerization product of the nonisolable ketene **11**, the initial product of the thermal degradation reaction, and due to its relative instability, fresh crops of the compound are usually required. Indenocarboxamides **3a**−**d** were prepared by treatment of oxetanone **12** with 2 equiv of the respective arylamine in CH_2Cl_2 in 82−85% yield.[16]

Indenocarboxamide **3a** was oxidized overnight with 1.5 equiv of PIFA in CH_2Cl_2 at 0 °C and three products, namely indenodiazepinone **4a**, indenopyrazolinone **5a**, the predicted oxidative cyclization products, and α-hydroxyamide **15a** (Scheme 5) were obtained in 50%, 15%, and 12% yield, respectively. α-Hydroxyamide **15a** is a byproduct resulting

SCHEME 4. Preparation of the Starting Indenonarboxamides 3



a: Ar = *p*-tolyl
b: Ar = Ph
c: Ar = *p*-Cl-C_6H_4
d: Ar = *p*-MeO-C_6H_4
e: Ar = Ph, Ar^1 = *p*-tolyl
f: Ar = *p*-Et-C_6H_4, Ar^1 = *p*-tolyl
g: Ar = *o*-tolyl, Ar^1 = *p*-tolyl
h: Ar = 2,4-di-Me-C_6H_4, Ar^1 = p-tolyl
i: Ar = *p*-Cl-C_6H_4, Ar^1 = *p*-tolyl
j: Ar = *p*-tolyl, Ar^1 = *p*-Cl-C_6H_4
k: Ar = *p*-tolyl, Ar^1 = Ph
l: Ar = *p*-tolyl, Ar^1 = mesityl
m: Ar = *m*-MeO-C_6H_4, Ar^1 = *p*-tolyl
n: Ar = *p*-NO_2-C_6H_4, Ar^1 = *p*-tolyl

from the oxidation of the amide functionality through an alternative pathway that will be discussed below. When the reaction was performed at room temperature, the yields of the desired cyclization products **4a** and **5a** improved to 68% and 16%, respectively (Table 1, entry 1). Reducing of the stoichiometric amount of the oxidant (1.1 equiv) resulted only in partial conversion of the starting material.

The conditions giving the best results for **4a** (PIFA 1.5 equiv, rt, CH_2Cl_2) were then applied to indenocarboxamides **3b**−**d**. The reaction of compound **3d** was rather unproductive. Indenodiazepinone **4d** was the only product isolated in poor 14% yield along with a complex mixture of products (Table 1, entry 4). The low yield of the desired oxidation products in this case could be attributed to a competitive oxidation process that can possibly take place on the enriched aromatic rings, as has already been mentioned.[20] In the cases of indenocarboxamides **3b**,**c** and despite the high total yield (73−84%) of the oxidation products, the desired indenodiazepinones **4b** and **4c** were obtained in 30% and 23% yield, respectively (Table 1, entries 2 and 3). α-Hydroxyamides **15b** and **15c** were the main reaction products, in 54% and 50% yield, respectively. On the basis of previously accepted mechanisms,[7−13] the presence of a proper neighboring group, such as an aryl-, alkoxy-, or nitrogen-containing group on the amide nitrogen atom, able to stabilize the positively charged acylnitrenium intermediate (Scheme 1), is usually required for the success of the reported PIFA-promoted amide oxidations. For the intramolecular trapping of this electron-deficient intermediate the presence of a nucleophilic counterpart is considered crucial. The increase in nucleophilicity of this functionality implies facilitation of the cyclization. Taking into account these assumptions and estimating that the amide group was almost quantitatively oxidized in the cases of compounds **3b** and **3c**, we reasonably

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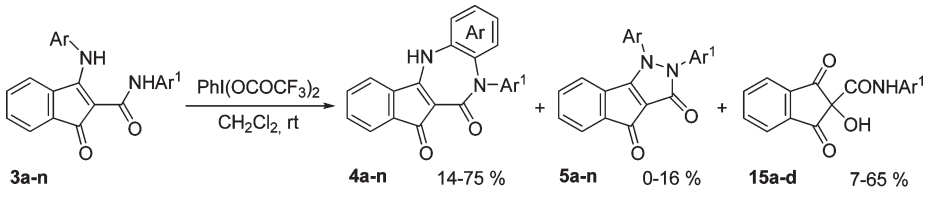
(20) Reference 1a, p 218; ref 1c, p 44.

TABLE 1. Yields of Isolated Products from the Oxidation of Enaminoamides 3

			products (yield, %)		
entry		starting enaminoamide **3**	indenodiazepinones **4**	indenopyrazolinones **5**	α-hydroxyamides **15**
1	**3a**	Ar = *p*-tolyl	**4a** (68)	**5a** (16)	**15a** (7)
2	**3b**	Ar = Ph	**4b** (30)	**5b** (0)	**15b** (54)
3	**3c**	Ar = *p*−ClC_6H_4	**4c** (23)	**5c** (0)	**15c** (50)
4	**3d**	Ar = *p*-$MeOC_6H_4$	**4d** (14)	**5d** (0)	
5	**3e**	Ar = Ph, Ar^1 = *p*-tolyl	**4e** (43)	**5e** (3)	**15a** (24)
6	**3f**	Ar = *p*-EtC_6H_4, Ar^1 = *p*-tolyl	**4f** (74)	**5f** (11)	**15a** (12)
7	**3g**	Ar = *o*-tolyl, $\mathbf{Ar^1}$ = *p*-tolyl	**4g** (26, 41)	**5g** (10, 15)	**15a** (21, 18)
8	**3h**	Ar = 2,4-di-MeC_6H_3, Ar^1 = *p*-tolyl	**4h** (57) [b]	**5h** (14)	**15a** (10)
9	**3i**	Ar = *p*-ClC_6H_4, Ar^1 = *p*-tolyl	**4i** (42)	**5i** (4)	**15a** (31)
10	**3j**	Ar = *p*-tolyl, Ar^1 = *p*-ClC_6H_4	**4j** (65)	**5j** (5)	**15c** (15)
11	**3k**	Ar = *p*-tolyl, Ar^1 = Ph	**4k** (75)	**5k** (8)	**15b** (17)
12	**3l**	Ar = *p*-tolyl, Ar^1 = mesityl	**4l** (24)[a]	**5l** (0)	**15d** (11)
13	**3m**	Ar = *m*-$MeOC_6H_4$, Ar^1 = *p*-tolyl	**4m** (35)[a]	**5m** (0)	**15a** (21)
14	**3n**	Ar = *p*-$NO_2C_6H_4$, Ar^1 = *p*-tolyl	**4n** (25)	**5n** (0)	**15a** (65)

[a]Starting material **3g** (23%), **3l** (45%), or **3m** (8%) was recovered unchanged under the usual reaction conditions. [b]Yields when 2.0 equiv of PIFA was used and all the starting enaminoamide was consumed.

SCHEME 5. PIFA-Mediated Oxidation of Indenocarboxamides 3



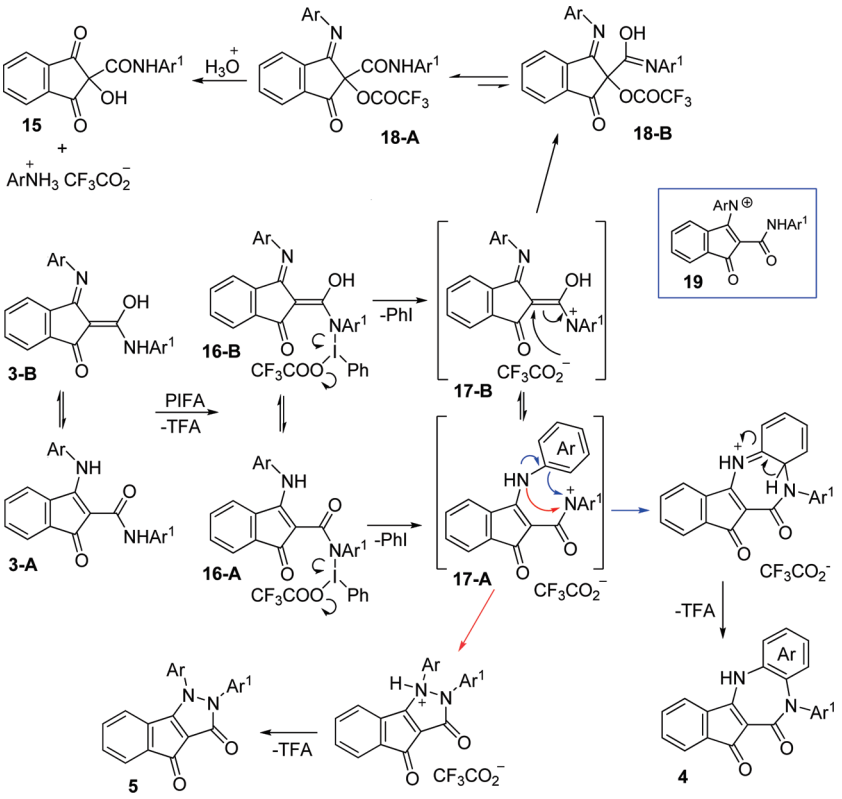
3, 4, 5a: Ar = *p*-tolyl
b: Ar = Ph
c: Ar = *p*-Cl-C_6H_4
d: Ar = *p*-MeO-C_6H_4
e: Ar = Ph, Ar^1 = *p*-tolyl
f: Ar = *p*-Et-C_6H_4, Ar^1 = *p*-tolyl
g: Ar = *o*-tolyl, Ar^1 = *p*-tolyl
h: Ar = 2,4-di-Me-C_6H_3, Ar^1 = p-tolyl
i: Ar = *p*-Cl-C_6H_4, Ar^1 = *p*-tolyl
j: Ar = *p*-tolyl, Ar^1 = *p*-Cl-C_6H_4
k: Ar = *p*-tolyl, Ar^1 = Ph
l: Ar = *p*-tolyl, Ar^1 = mesityl
m: Ar = *m*-MeO-C_6H_4, Ar^1 = *p*-tolyl
n: Ar = *p*-NO_2-C_6H_4, Ar^1 = *p*-tolyl
15a: Ar^1 = *p*-tolyl
b: Ar^1 = Ph
c: Ar^1 = *p*-Cl-C_6H_4
d: Ar^1 = mesityl

assumed that the deviation from the desired oxidative cyclization could rather be attributed to the relatively diminished donating properties of the phenyl and *p*-chlorophenyl groups of the nucleophilic arylamino (ArNH) moiety, in respect to the *p*-tolylamino group in **3a**.

Therefore, in order to get more information and determine the scope of the proposed cyclization with respect to the amine functionality, we decided to explore the influence of the nature of the aryl substituent of the ArNH group on the efficiency of the cyclization step. For this purpose and selecting the *p*-tolyl group as the optimal substituent for the amide nitrogen atom, a series of indenocarboxamides **3e**−**n** differently substituted at the two *N*-aryl rings of the amine (*N*-Ar) and the amide (*N*-Ar^1) groups were prepared. This can be accomplished by the successive treatment of oxetanone **12** with two different arylamines (1 equiv each time). The reaction of oxetanone **12** with 1 equiv of arylamine is known to produce the enaminoesters **14** that can be isolated in good yields by crystallization (Scheme 4).[16] Treatment of the enaminoesters **14** with one more equivalent of the arylamine leads to indenocarboxamides **3**. By implementation of this process and using aniline, *p*-ethylaniline, *o*-toluidine, 2,4-dimethylaniline, *p*-chloroaniline, *p*-nitroaniline, or *m*-anisidine in the first step and *p*-toluidine in the second one, indenocarboxamides **3e**−**i**,**m**,**n**, were prepared in 53−76% total yield for the two steps.

As shown in Table 1, the outcome of the reactions of these indenocarboxamides with PIFA indicates a significant dependence on the substituents of the arylamino (ArNH) fragment. More specifically, the PIFA-mediated oxidations of indenocarboxamides **3f**−**h** bearing activated alkyl-substituted phenyl rings afforded good to excellent total yields of the target cyclization products **4f**−**h** (41−74%) and **5f**−**h** (11−15%) and low yields (10−18%) of the byproduct **15a** (entries 6−8). The lower yield (41%) of indenodiazepinone **4g** with respect to that of **4f** (74%) could be attributed to both the loss of one ortho active site of the aryl ring and the steric effects of the ortho methyl substituent. On the other hand, the effectiveness of the reaction of 2,4-dimethylphenylaminoindenocarboxamide **3h**, that afforded better yields (57%) of indeno-diazepinone **4h**, is ascribed to the increased electron-donating properties of the 2,4-dimethylphenyl group compared to those of the tolyl group (in carboxamide **4g**) that can counterbalance the steric effect of the ortho substituent. In accordance with this, the outcome of the reactions of the substrates bearing a nonactivated phenyl (**3e**, entry 5), a moderately deactivated *p*-chlorophenyl (**3i**, entry 9), or a strongly deactivated *p*-nitrophenyl group (**3n**, entry 14) is predictable. Indeed, indenodiazepinones **4e** and **4i** were obtained in moderate yields (43% and 42%) from the reactions of the corresponding indenocarboxamides **3e** and **3i**, whereas the yield of the isolated corresponding product **4n** was considerably lower (25%). In these cases, the yield of α-hydroxyamide **15a** gradually increased (24%, 31%, and 65% from **3e**, **3i**, and **3n**, respectively) in a retrograde to the activation of the arylamino (ArNH) group manner. Our

SCHEME 6. Proposed Mechanistic Pathway for the Formation of Diazepinones 4, Pyrazolinones 5, and α-Hydroxyamides 15



assumption was also verified by the results of the PIFA-mediated reactions of indenocarboxamides **3j** and **3k** (Table 1, entries 10 and 11). The yields of indenodiazepinones **4j** and **4k** (65% and 75%) compared to those of **4c** and 4b (23% and 30%), derived from the oxidations of indenocarboxamides **3c** and **3b**, reflect the reinforcement of the electron-donating properties of *p*-tolyl group in respect to those of the *p*-chlorophenyl or phenyl group in **3c** and **3b**. Once again, the poor yield of the desired **4m** from the reaction of methoxy-substituted indenocarboxamide **3m** with PIFA (Table 1, entry 13) could probably be ascribed to byproducts resulting from a contemporary oxidation of the enriched aromatic ring. Finally, the effect of the bulky mesityl substituent on the oxidation of the amide group is obvious in the case of indenocarboxamide **3l** (Table 1, entry 12) where the product yields are notably reduced.

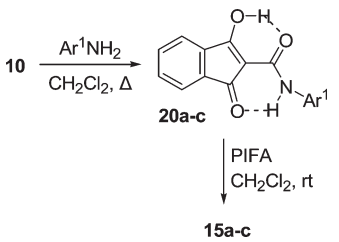
The above results are consistent with the plausible mechanistic proposal described in Scheme 6. Initially, the amide group of indenocarboxamide **3**, known to exist in solution in two tautomeric forms **3-A** and **3-B**,[16] reacts with PIFA to give intermediate **16**, which is then transformed to the acylnitrenium ion **17** via an oxidative process. The acylnitrenium ion reacts intramolecularly with the nucleophilic aryl (Ar) group to furnish eventually the fused indenobenzodiazepinones **4** through abstraction of TFA. Alternative intramolecular nucleophilic attack of the nitrogen atom of the ArNH fragment on the nitrenium active center followed again by TFA abstraction produces pyrazolinones **5**. The lower efficiency of the latter pathway, impressed in the yields of pyrazolinones **5**, is undoubtedly ascribed to the limited nucleophilicity of this nitrogen atom due to its amidic nature (vinylogous amide). Regarding α-hydroxyamide **15**, it originates from the common intermediate **17** which is attacked by the trifluoroacetate anion delivered by PIFA, as depicted in Scheme 6. Both the ester and the arylimino (ArN=) group of the intermediate **18** are probably hydrolyzed during workup. Alternatively, a PIFA-promoted oxidative degradation of the arylimino group[21] could not be excluded, although the anticipated oxidation product ArN=NAr, formal product from the dimerization of nitrene [ArN:], of such a process has never been isolated.

An alternative pathway based on the acceptance that PIFA reacts initially with the ArNH group and the amide *N*-aryl substituent (Ar^1NH) attacks the generated electron-deficient center in **19** could rather be excluded. In this case, structurally different diazepinones, fused with the Ar^1 ring and having the substituent Ar on nitrogen, would be formed. Such products were never isolated, and moreover, the reaction of indenocarboxamide bearing a bis-ortho-substituted arylamino group (Ar = mesityl, Ar^1 = *p*-tolyl) with PIFA failed to give any cyclization products, the only isolated product being α-hydroxyamide **15a**.

Structure elucidation of compounds **4**, **5**, and **15** was based on their analytical and spectral data. The most discernible difference in the ^{1}H NMR spectra of indenodiazepinones **4** and pyrazolinones **5** is the absence of the peak for one of the ortho protons of the arylamino (ArNH) group, as well as the appearance of a broad singlet at δ 11.22−11.91 for the −NH group in the spectra of compounds **4**. Due to the difficulty of chromatographic separation of pyrazolinones **5** from hydroxyamides **15**, no satisfactory ^{13}C NMR spectra could be

(21) Reference 1a, p 98.

SCHEME 7. Independent Preparation of α-Hydroxyamides 15



measured for some pyrazolinones **5**, such as **5i** and **5j** obtained in very low yields.

Regarding α-hydroxyamides **15**, their structure was further verified through their independent synthesis based on the PIFA-mediated oxidation of indanedionecarboxamides **20** (Scheme 7). The latter can arise from the thermal degradation of phenyliodonium ylide **10** curried in the presence of 1 equiv of arylamine.[22] The oxidation reactions of amides **20** were performed under the previously applied conditions for the oxidation of amides **3** furnishing α-hydroxyamides **15** in 66−85% yield. In this case as there is no second arylamino group in the molecule, carboxamides **20** are inevitably converted to α-hydroxyamides **15**.

Since the prepared diazepinones **4** are new templates they were tested for possible biological activity, at a first level. Nine selected derivatives, namely **4a**−**c**,**e**,**g**,**i**−**k**,**m**, were screened for their antioxidant activity, according to a reported methodology[23] and more specifically for their reducing ability determining their interaction percent values with the stable radical 1,1-diphenylpicrylhydrazyl (DPPH) and for their inhibition of soybean lipoxygenase, as well as for their inhibitory activity on the lipid peroxidation of linoleic acid. Compounds **4m** and **4j** showed significant reducing activity (83% and 78%, respectively, compared to 81% of the nordihydroguaeretic acid used as a reference compound). Diazepinones **4b**, **4e**, and **4k** were found to be the more potent inhibitors of soybean lipoxygenase (IC_{50} values 50, 29.5, and 50 μM, respectively, compared to the 600 μM, the IC_{50} value of caffeic acid, which was used as a standard). Derivative **4b** inhibits lipid peroxidation more effectively (88%) in comparison to trolox (63%), used as a standard. Almost all the screened compounds present antioxidant activities as indicated (Table) in the Supporting Information. These preliminary results seem promising. Further investigation is in progress in order to delineate the possible mechanism of action of these new compounds.

Conclusions

In conclusion, the preparation of fused indenodiazepinones **4**, new templates with possible biological activity, through the oxidation of indenocarboxamides **3**, is reported in this paper. The yields of **4** compared to the yields of the two other products of the reaction **5** and **15**, in correlation to the nature of the substituents on both aromatic rings, give evidence for the reaction pathway. Indenodiazepinones **4** are accessed by a sequence of reactions where two of the most known hypervalent iodine reagents, $PhI(OCOCH_3)_2$ and $PhI(OCOCF_3)_2$, play a crucial role: the former for the preparation of phenyliodonium ylide of lawsone and the latter for the final oxidation and hence the title of this paper.

Experimental Section

Preparation of Indenocarboxamides 3a−d. These amides were prepared by addition of 2 equiv of arylamine to a stirred suspension of oxetanone **12** in CH_2Cl_2 according to the previously reported method, in 82−85% yield.[16]

Preparation of Indenocarboxamides 3e−n. These amides having different aryl groups were prepared by sequential addition of 1 equiv of a different arylamine each time to a stirred suspension of oxetanone **12** in CH_2Cl_2 in analogy to the previously reported method.[16]

Typical Procedure for the Preparation of Indenocarboxamide 3e. Aniline (0.5 mmol) dissolved in CH_2Cl_2 (2 mL) was added to a stirred suspension of oxetanone **12** (0.5 mmol) in CH_2Cl_2 (5 mL), and stirring was continued for 1 h. Hexanes (∼2 mL) was added to the reaction solution to effect precipitation, and the resulting yellow solid was filtered, dried, and used for the next step without further purification (yield of the crude product 86%). The enaminoester **14e** (0.4 mmol) obtained in this manner was dissolved in CH_2Cl_2 (5 mL), *p*-toluidine (0.4 mmol) was added, and the resulting suspension was stirred at room temperature for 4 h. The precipitated 2,3-dihydroxy-1,4-naphthoquinone (**13**) was filtered off, and the filtrate was concentrated and chromatographed on column (silica gel, hexanes−ethyl acetate 5:1 up to 3:1) to afford **3-anilino-*N*-(4-methylphenyl)-1-oxo-1*H*-indene-2-carboxamide (3e)** in 66% yield: mp 189−191 °C; IR (KBr) cm^{-1} 1671, 1644; ^1H NMR ($CDCl_3$, 300 MHz) δ 11.99 (brs, 1H), 10.07 (brs, 1H), 7.62−7.53 (m, 3H), 7.53−7.45 (m, 3H), 7.45−7.35 (m, 3H), 7.19−7.07 (m, 3H), 6.47 (d, J = 7.7 Hz, 1H), 2.33 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 189.6, 169.1, 165.1, 137.1, 135.9 134.4, 133.2, 132.6, 131.6, 129.7, 129.5, 128.7, 126.6, 124.2, 121.9, 120.0, 98.2, 20.9; ESI-HRMS m/z calcd for $C_{23}H_{18}N_2O_2$ + Na (MNa^+) 377.12605, found 377.12616.

Typical Procedure for the Oxidation of Indenocarboxamide 3a. A solution of PIFA (0.3 mmol) in CH_2Cl_2 (5 mL) was added during a period of 30 min to a stirred solution of indenocarboxamide **3a** (0.2 mmol) in CH_2Cl_2 (15 mL), and the reaction was monitored by TLC. After the disappearance of indenocarboxamide **3a** (4−5 h), the reaction mixture was washed successively with saturated solutions of $NaHCO_3$ and NaCl and dried with Na_2SO_4. The dried solution was concentrated and chromatographed on column using silica gel and hexanes-ethyl acetate 3:1 for the elution of iodobenzene and diazepinone **4a**, gradually increasing to 1:1 for the elution of hydroxyamide **15a** and finally pure ethyl acetate for the elution of pyrazolinone **5a**. Since partial decomposition of **4a** is observed on the column during prolonged chromatography time, it is better to perform chromatography separation as soon as possible even if that implies a second column chromatography for the complete separation of **15a** and **5a**. Isolated in order of eluance:

9-Methyl-7-(4-methylphenyl)-7,12-dihydrobenzo[*b*]indeno-[1,2-*e*][1,4]diazepine-5,6-dione (4a). 68% yield; mp 205−208 °C; IR (KBr) cm^{-1} 1660, 1634; ^1H NMR ($CDCl_3$, 300 MHz) δ 11.88 (brs, 1H), 8.02 (d, J = 7.3 Hz, 1H), 7.76 (d, J = 6.7 Hz, 1H), 7.65−7.52 (m, 2H), 7.40−7.22 (m, 5H), 6.99 (d, J = 8.5 Hz, 1H), 6.66 (s, 1H), 2.40 (s, 3H), 2.29 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 189.7, 162.2, 161,9, 146.4, 141.7, 138.7, 138.6, 136.1, 136.0, 132.9, 132.8, 132.5, 131.0, 129.9, 127.7, 123.1, 121.6, 121.53, 121.47, 93.0, 21.0, 20.7; ESI-HRMS m/z calcd for $C_{24}H_{18}N_2O_2$ + H (MH^+) 367.14410, found 367.14405.

2-Hydroxy-*N*-(4-methylphenyl)-1,3-dioxoindane-2-carboxamide (15a). 7% yield; mp 140−142 °C; IR (KBr) cm^{-1} 3345, 1757, 1716, 1666; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.78 (brs, 1H),

(22) Malamidou-Xenikaki, E.; Spyroudis, S.; Tsanakopoulou, M. *J. Org. Chem.* **2003**, *68*, 5627.

(23) (a) Kontogiorgis, C.; Hadjipavlou-Litina, D. *J. Enzym. Inhib. Med. Chem.* **2003**, *18*, 63. (b) Liegois, C.; Lermusieau, G.; Colin, S. *J. Agric. Food Chem.* **2000**, *48*, 1129.

8.06−7.98 (m, 2H), 7.93−7.87 (m, 2H), 7.34 (d, J = 8.3 Hz, 2H), 7.06 (d, J = 8.3 Hz, 2H), 2.28 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 194.8, 163.5, 142.6, 136.7, 134.9, 133.8, 129.5, 124.3, 119.8, 82.4, 20.9; ESI-HRMS m/z calcd for $C_{17}H_{13}NO_4$ + H (MH^+) 318.07361, found 318.07360.

1,2-Bis(4-methylphenyl)-1,2-dihydroindeno[1,2-*c*]pyrazole-3,4-dione (5a). 16% yield; mp 253−255 °C; IR (KBr) cm^{-1} 1720, 1666; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.67 (d, J = 7.4 Hz, 1H), 7.42 (t, J = 7.4 Hz, 1H), 7.33−7.24 (m, 5H), 7.11 (s, 4H), 6.88 (d, J = 7.4 Hz, 1H), 2.39 (s, 3H), 2.28 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 181.8, 163.4, 157.9, 141.1, 140.8, 138.6, 132.35, 132.29, 132.1, 131.6, 130.6, 130.3, 129.9, 127.0, 126.4, 124.2, 120.8, 104.8, 21.4, 21.2; ESI-HRMS m/z calcd for $C_{24}H_{18}N_2O_2$ + H (MH^+) 367.14410, found 367.14424.

Typical Procedure for the Preparation of α-Hydroxycarboxamide 15a from Oxidation of Indanedionecarboxamide 20a. Indanedionecarboxamide **20a** was prepared from the thermal decomposition of iodonium ylide of lawsone **10** in the presence of *p*-toluidine in 94% yield, as it was described.[22]

A solution of PIFA (0.24 mmol) in CH_2Cl_2 (5 mL) was added to a stirred solution of indanedionecarboxamide **20a** (0.2 mmol) in CH_2Cl_2 (15 mL), and the reaction was monitored by TLC. After the disappearance of indandionecarboxamide **20a** (2−3 h), the reaction mixture was washed successively with saturated solutions of $NaHCO_3$ and NaCl and dried with Na_2SO_4. The dried solution was concentrated and chromatographed on column using silica gel and hexanes−ethyl acetate from 3:1 to pure ethyl acetate. The colorless hydroxyamide **15a** was isolated after iodobenzene in 66% yield and it was in all respects identical to α-hydroxycarboxamide **15a** isolated as the minor product in the previously described oxidation reaction of indenocarboxamide **3a**.

Supporting Information Available: Spectral and analytical data for all new compounds **3b**,**e**−**n**, **4a**−**n**, **5a**,**e**−**k**, and **15a**−**d** and the results of biological tests. This material is available free of charge via the Internet at http://pubs.acs.org.