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Indium-Promoted Allylation Reaction of Imino-Isatins in Aqueous Media: Synthesis of Quaternary 3-Aminooxindoles

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Keywords: Synthetic methods / Indium / Allylation / Nitrogen heterocycles

Quaternary 3-amino-2-oxindoles have been obtained via allylation and propargylation reactions of imino-isatins in aqueous media promoted by In and Zn respectively, under Barbier conditions, in good to excellent yields. A quaternary new stereocenter has been formed without hydrolysis of the starting imino-isatin.

Introduction

The presence of the 3,3-disubstituted oxindole skeleton in various natural products and biologically active compounds has stimulated considerable attention to the development of novel strategies for their preparation.[1] In particular, the 3-substituted 3-amino-2-oxindole framework is present in the potent gastrin/CCK-B receptor antagonist AG-041R (**1**),[2] the vasopressin VIb receptor antagonist SSR-149415 (**2**),[3] and the family of natural products chartellines (e.g., chartelline C, **3**)[4] (Figure 1), among others.

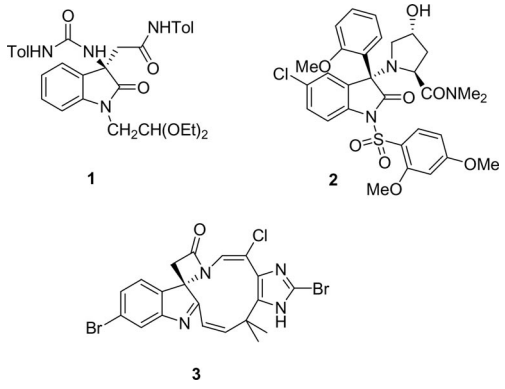

Figure 1. Bioactive quaternary aminooxindoles.

Preparation of quaternary 3-aminooxindoles has been achieved following several strategies including alkylation of 3-aminooxindoles,[5] substitution of 3-chlorooxindoles by amines,[6] from 3-ylideneoxindoles,[7] [2+2] cycloadditions of isatin-derived azomethine ylides,[8] radical addition,[9] amination of 2-oxindoles,[10] Grignard addition to imines,[11] and oxidative intramolecular aza-spiroannulation.[12]

On the other hand, the appealing properties of organometallic reactions in aqueous media include their synthetic advantages (many reactive functional groups, such as hydroxy, amine, and carboxylic functions, do not require the protection-deprotection protocol in such reactions, and many water soluble compounds do not need to be converted into their derivatives and can be reacted directly), its potential as an environmentally benign chemical process (the use of anhydrous flamable solvents can be avoided and the burden of solvent disposal may be reduced), as well as unique reactivity and selectivity that are not often attained under dry conditions, making then profitable in many cases.[13] Indium has emerged as the metal of choice to mediate a high number of transformations in aqueous media, because of its enviromentally benign properties allied with a high degree of chemo-, regio- and diastereoselectivity.[14] In this context, addition to C=N[15] bonds offers an excellent opportunity for the development of new carbon–carbon bond preparation of nitrogen-containing compounds.[16]

Previously, we have reported the metal-mediated carbonyl-addition/cyclization reaction sequences in isatins.[17] In connection with our current research interest in the preparation of biologically relevant nitrogenated compounds,[18] we wish to describe herein the allylation of imines derived from isatins in aqueous media promoted by indium.

Results and Discussion

The starting materials, imino compounds derived from isatins **4a**–**e**, were efficiently prepared by condensation reaction with tosylhydrazine, 1,1-diphenylhydrazine, benzoylhydrazine and *p*-anisidine, respectively, following procedures described in the literature (Figure 2).[19]

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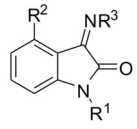
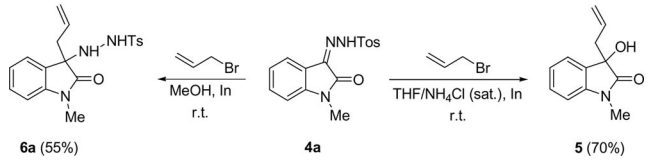


4a R^1 = Me, R^2 = H, R^3 = NHTos
4b R^1 = Me, R^2 = H, R^3 = NPh_2
4c R^1 = Me, R^2 = H, R^3 = NHCOPh
4d R^1 = H, R^2 = H, R^3 = PMP
4e R^1 = H, R^2 = Br, R^3 = PMP
4f R^1 = Bn, R^2 = H, R^3 = PMP

Figure 2. Starting imines **4a**–**f** derived from isatins (PMP = 4-MeO-C_6H_4).

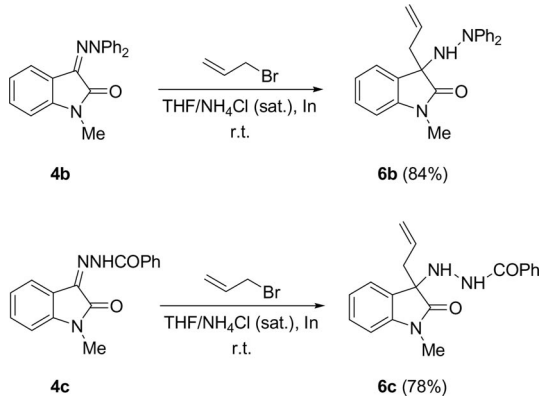
Initially we explored the allylation reaction of tosylhydrazone derived isatin **4a** in aqueous media promoted by indium. Treatment of a THF/NH_4Cl (aq. saturated) solution of compound **4a** with allyl bromide in the presence of indium, using the same optimum conditions that we described previously for allylation reactions of isatins and β-lactams,[17,20] afforded compound **5** derived from hydrolysis of the starting tosylhydrazone **4a** followed by carbonyl-allylation (Scheme 1). Several attempts to obtain the allylation reaction of the C=N bond in aqueous media, including addition of additives ($HfCl_4$ or $InCl_3$), without hydrolysis of the tosylhydrazone group were unsuccessful. Fortunately, imino-allylation of tosylhydrazone **4a** was achieved when the reaction was performed in MeOH as solvent, affording 3-amino-2-oxindole **6a** in 55% yield (Scheme 1).



Scheme 1. Allylation reaction of tosylhydrazone **4a** in anhydrous and aqueous media.

We then turned our attention to hydrazones **4b** and **4c**. Thus, treatment of compounds **4b** and **4c** under the conditions described above afforded products **6b** and **6c**, respectively, in good yields (Scheme 2).

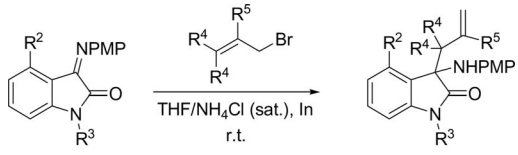
These preliminary results encouraged us to screen the indium-promoted allylation of imines **4d**–**f** derived from *p*-anisidine. Under the optimized conditions, allylation product **6d** was obtained in 54% yield (see Table 1, entry 1). Since the incorporation of water stable additives could improve both yield and conversion rate, we explored further the indium-promoted allylation of imine **4d** in the presence of different additives. The addition of catalytic quantity of hafnium(IV) chloride afforded compound **6d** in very low yield (Table 1, entry 2). Fortunately, the addition of indium(III) chloride (cat.) accelerated the process, affording the 3-amino-3-allyl-2-oxindoles **6d** and **6e** in fair yields (85% and 54%, respectivelly) after 1 h (Table 1, entries 3 and 4). Although the role of the $InCl_3$ as additive is not completely understood, it may be explained in terms of



Scheme 2. Allylation reaction of tosylhydrazone **4b** and **4c** in aqueous media.

Lewis acid which activates both the imine group as well as the softness of the allylmetal reagents. A transmetallation of the initially formed organometallic reagent with indium(III) chloride as Lewis acid may be involved. Due to the importance of the presence of a catalytic amount of additive in the reaction, allylation of imine **4d** was investigated using different additives (silver trifate, zinc iodide, silver acetate and bismuth trichloride). In the event, the expected allylated product **6d** was obtained in good to excellent yields in all cases (Table 1, entries 5–9, 11, and 14). Analogous results were obtained for the indium-mediated allylation reactions on using imino-isatins **4d**–**f** in the presence of prenyl bromide or 3,3-dimethylallyl bromide (Table 1, entries 10–14).

Table 1. Allylation reaction of imino-isatins **4d**–**f** under aqueous conditions.



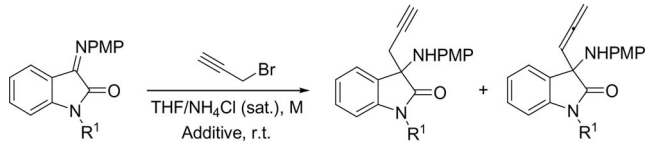
Entry	Imine	R^2	R^3	R^4	R^5	Additive (2 mol-%)	t [h]	Product	Yield [%][a]
1	**4d**	H	H	H	H	–	24	**6d**	54
2	**4d**	H	H	H	H	$HfCl_4$	3	**6d**	17
3	**4d**	H	H	H	H	$InCl_3$	1	**6d**	85
4	**4e**	Br	H	H	H	$InCl_3$	1	**6e**	54
5	**4d**	H	H	H	H	TfOAg	1	**6d**	90
6	**4d**	H	H	H	H	ZnI_2	1	**6d**	82
7	**4d**	H	H	H	H	AcOAg	1	**6d**	78
8	**4d**	H	H	H	H	$BiCl_3$	3	**6d**	75
9	**4f**	H	Bn	H	H	AcOAg	1	**6f**	87
10	**4d**	H	H	H	Me	$InCl_3$	3	**6g**	40
11	**4f**	H	Bn	H	Me	AcOAg	1	**6h**	72
12	**4d**	H	H	Me	H	$InCl_3$	2	**6i**	87
13	**4e**	Br	H	Me	H	$InCl_3$	1	**6j**	61
14	**4f**	H	Bn	Me	H	AcOAg	1	**6k**	77

[a] Yield of pure, isolated product with correct analytical and spectroscopic data. [b] PMP = 4-MeO-C_6H_4.

Having established the optimal reaction conditions to carry out the allylation reaction, our next aim was to evaluate the feasibility of other related metal-mediated Barbier-type reactions in imino-isatins, studying the regiochemistry of the connection (e.g., allenylation vs. propargylation). However, it is not easy to control selectivity between Barbier-type propargylation and allenylation with propargyl halides. The reaction of propargyl bromide with metals has been proposed to generate an equilibrium between the allenyl and propargyl organometallics. Both organometallic species can react with the C=N bond affording a mixture of two regioisomers, namely, homopropargyl and allenylamines. The regioselectivity of the carbon–carbon bond formation was initially investigated through the metal-promoted reaction between tosylhydrazone **4a** and propargyl bromide in anhydrous methanol, however, in the event only starting material was recovered. Unfortunately, the same behavior was observed when hydrazones **4b** and **4c** were treated under both aqueous and anhydrous conditions. Thus, we turned our attention to the indium-promoted reaction between imino-isatin **4d** and propargyl bromide in THF/NH_4Cl (aq. saturated) in the presence of $HfCl_4$ at room temperature. In the event, the 3-substituted 3-aminooxindole moiety was obtained after 2 days of reaction; however, the observed regioselectivity was poor (75:25) in favor of the propargylic product. The use of other additives (TfOAg, $SnCl_2{\cdot}H_2O$/LiI or AcOAg) increased the amount of the ratio **7/8** in favor of the propargylated product (Table 2, entries 2, 4 and 5). Only, when the indium-promoted propargylation of imino-isatin **4d** was tested using a small amount of ZnI_2 the corresponding propargylated product **7a** was obtained as a single regioisomer (Table 2, entry 3). Interestingly, the zinc-induced reaction, using a catalytic amount of additive ($HfCl_4$) afforded after 18 h 3-amino-3-propargyl-2-oxindole (**7a**) as single isomer in good yield (86%). The use of other additives has been tested for the propargylation reaction. Among all additives studied, the use of a catalytic amount of ZnI_2, AcOAg or $BiCl_3$ did not improve the reaction time and/or the yield (see Table 2, entries 8–10). However, when a small amount of TfOAg was added to the reaction mixture, the propargylated product **7a** was obtained in just one hour in excellent yield (90%) (Table 2, entry 7).

Unfortunately, attempted experiments to find an efficient allenylation method by the use of 3-substituted 2-propynyl bromides (1-bromo-2-butyne and 3-bromo-1-phenylpropyne) did not provide the corresponding 3-allenyl-3-aminooxyindoles of type **8**. The metal promoters used were indium or zinc in presence of a small amount of additive ($HfCl_4$, $InCl_3$, $BiCl_3$, ZnI_2, TfOAg, $SnCl_2{\cdot}H_2O$/LiI or AcOAg), obtaining in all cases a complex mixture of reaction. Interestingly, treatment of imino-isatin **4d** with 1-bromo-2-butyne, indium powder (1.56 mmol), $InCl_3$ (0.03 mmol) and CuI (1.04 mmol) in methanol/water (1:1),[21] cleanly afforded the propargylated compound **9** in 45% yield (Scheme 3). However, when the same reactions conditions were applied to the reaction of imino-isatin **4d** with 3-bromo-1-phenylpropyne, only a complex crude was obtained.

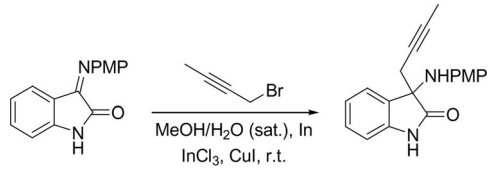
Table 2. Propargylation reaction of imino-isatins **4d** and **4f** under aqueous conditions.



4 **7** **8**

Entry	Imine	R^1	M	Additive (2 mol-%)	*t* [h]	Ratio **7/8**	Product	Yield [%][a]
1	**4d**	H	In	$HfCl_4$	48	75:25	**7a**	75
2	**4d**	H	In	TfOAg	18	90:10	**7a**	87
3	**4d**	H	In	ZnI_2	18	100:0	**7a**	40
4	**4d**	H	In	AcOAg	18	90:10	**7a**	72
5	**4d**	H	In	$SnCl_2{\cdot}2H_2O$ LiI	18	90:10	**7a**	77
6	**4d**	H	Zn	$HfCl_4$	18	100:0	**7a**	86
7	**4d**	H	Zn	TfOAg	1	100:0	**7a**	90
8	**4d**	H	Zn	ZnI_2	18	100:0	**7a**	85
9	**4d**	H	Zn	AcOAg	18	100:0	**7a**	83
10	**4d**	H	Zn	$BiCl_3$	18	100:0	**7a**	78
11	**4f**	Bn	Zn	AcOAg		100:0	**7b**	85

[a] Yield of pure, isolated product with correct analytical and spectroscopic data. [b] PMP = 4-MeO-C_6H_4; M = metal promoter.



4d **9** (45%)

Scheme 3. Propargylation reaction of imino-isatin **4d** in aqueous media.

Conclusions

In conclusion, we have achieved an efficient protocol for the preparation of quaternary 3-amino-2-oxindoles from imino-isatins. The Barbier-type allylation and propargylation reactions proceeds in aqueous environment under mild conditions promoted by indium and zinc respectively. In addition, it has been shown the importance of the use of additives in the reaction time, yield and the selectivity of the addition reactions.

Experimental Section

General Procedure for the Allylation Reaction of Isatins 4 Promoted by Indium in Aqueous Medium. Preparation of Compounds 6: Allyl bromide (2 mmol) was added to a well-stirred suspension of the corresponding isatin (1.0 mmol) and indium powder (229 mg, 2 mmol) in THF/NH_4Cl (aq. saturated) (1:1, 5 mL) at room temperature. After disappearance of the starting material (TLC), the mixture was extracted with ethyl acetate (3 × 5 mL). The organic extract was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue using ethyl acetate/hexanes mixtures gave analytically pure compounds **6**.

Supporting Information (see also the footnote on the first page of this article): Full spectroscopy and analytical data for previously unreported compounds not included in the Exp. Sect. Compound characterization data and experimental procedures for compounds **6**–**8**, as well as ^{1}H and ^{13}C NMR chemical shifts of representative hydrogen and carbon atoms of compounds **6**–**8**.

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