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PAPER

Synthesis of α-functionalized α-indol-3-yl carbonyls through direct S_N reactions of indol-3-yl α-acyloins

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A new and efficient synthesis of α-functionalized α-indol-3-yl ketones from easily available indolyl α-acyloins is reported. This process, catalyzed by Brønsted or Lewis acids, involves the uncommon direct nucleophilic substitution reaction of a secondary α-carbonyl-substituted hydroxyl group. The described methodology allows the introduction of a variety of nucleophiles such as (hetero)arenes, thiophenols, nitroanilines and 1,3-dicarbonyl derivatives. The synthesized α-indol-3-yl carbonyl compounds are important synthetic targets also useful for accessing functionalized tryptophols and furan-3-yl indoles.

Introduction

The importance of the indole nucleus, due to its ubiquity in natural and biologically active compounds, is cleared by the continuous development of methodologies for its synthesis and functionalization.[1] In this field, the preparation of indoles C3-substituted with a wide variety of functional groups continues attracting the interest of organic chemists.[2] Among them, α-(indol-3-yl) carbonyl compounds are relevant precursors for the preparation of biologically active molecules such as tryptamines,[3] β-carbolines and carbazoles,[4] and tryptophols,[5] which are found in several natural sources[6] and are useful intermediates in the synthesis of some biologically active compounds.[7] Different methodologies have been reported for accessing α-(indol-3-yl) carbonyl compounds, but most of them involve several steps or prefunctionalized starting materials.[8] Interestingly, direct approaches for the synthesis of α-(indol-3-yl) ketones from unprotected indoles and different carbonyl partners have been developed,[9] including the radical coupling of indoles with carbonyls [Scheme 1, Eq. (a)],[9a] the TBHP-mediated oxidative C–H activation of ketones [Scheme 1, Eq. (b)],[9b] and the addition of indoles to oxyallyl cations derived from ketones, independently developed by Chi[9c] and MacMillan[9d] [Scheme 1, Eq. (c)]. More recently, the dehydrative coupling of indoles with tertiary[9e,f] or secondary[9g] acyloins has been described under acid-catalysis [Scheme 1, Eq. (d)]. However, none of the available protocols allow the formation of α-functionalized α-(indol-3-yl) ketones as hydrogen or simple alkyl or aryl groups could be present at this α-position. On the other hand, arenesulfonyalkyllindoles[10] and 3-indolylmethanols[11] have been extensively used as reagents for accessing C3-substituted indoles through alkylideneindolenine or alkylideneindoleninium ion intermediates under basic or acidic conditions, respectively.[12] In this context, it has been reported that α-functionalized α-(indol-3-yl) ketones can be obtained by the reaction of *N*-alkyl ketosulfonyl indoles **1** with nucleophiles, such as silyl ketene acetals, using an excess of $AlEtCl_2$ as Lewis acid [Scheme 1, Eq. (e1)].[13] In the same way, α-aryl α-(indol-3-yl) ketones have been prepared by a Stetter-type cross coupling reaction of aldehydes with *N*-H 3-(1-arylsulfonylalkyl)indoles **2** in the presence of base and catalyzed by an *N*-heterocyclic carbene [Scheme 1, Eq. (e2)].[14] However, these strategies suffer from the use of stoichiometric amounts of Lewis acids or bases that clearly restricts their usefulness and general applicability. Therefore, the development of an efficient and general methodology for the synthesis of α-functionalized α-(indol-3-yl) ketones is highly desirable. Considering the likely generation of an alkylidenindolenine intermediate in the above reported procedures, we envisaged that a complementary approach to these α-indolyl ketones could involve the direct acid-catalyzed nucleophilic substitution of indol-3-yl α-acyloins **3** [Scheme 1, Eq. (f)]. Although several examples about indol-3-ylmethanols,[15] as precursors of alkylidenindolenine intermediates, and their subsequent reactions with nucleophiles have been reported in the literature,[11] the presence of the α-carbonyl group could disfavor the formation of the required iminium intermediate. Whereas catalytic Friedel–Crafts reactions of tertiary α-hydroxyesters or α-hydroxyketones, as well as α-acyloins, have been recently reported,[9e-g] to the best of our knowledge the use of indol-3-yl α-acyloins as alkylating agents for these processes have not been previously described.[16] Herein, and as part of our ongoing work in the acid-catalyzed S_N1-type reaction of π-activated alcohols,[17] we report our results in the synthesis of

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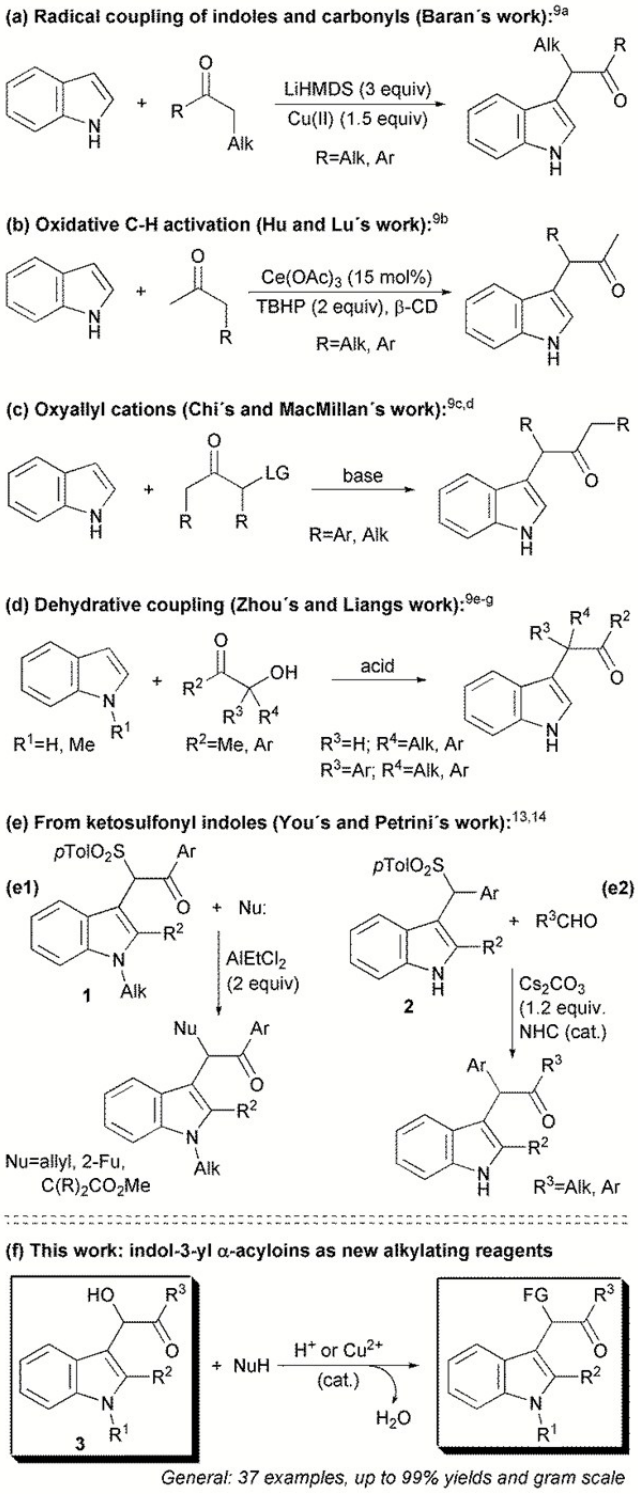
Electronic Supplementary Information (ESI) available: Experimental details, compound characterization, copies of ^1H and ^{13}C NMR spectra. See DOI: 10.1039/x0xx00000x



Scheme 1 Previous approaches to the synthesis of α-substituted α-(indol-3-yl) carbonyls and present work.

α-functionalized α-(indol-3-yl) ketones by Brønsted or Lewis acid-catalyzed direct nucleophilic substitution reactions.

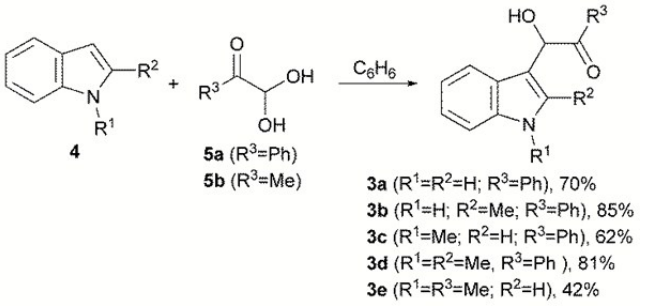
Results and discussion

Preparation of α-acyloins 3

To test our proposal, we needed to synthesize indol-3-yl α-acyloins **3**. The preparation of this type of compounds has been reported involving the reaction of π-excessive heterocycles such as indoles **4** with arylglyoxals like **5a**.[18] By conducting these reactions in the absence of any catalyst α-acyloins **3a-d** were isolated in high yields by simple filtration (Scheme 2).[19] In addition, although in moderate yield, we have also been able to prepare a new α-acyloin **3e** by treatment of *N*-methylindole **4c** with pyruvic aldehyde **5b** under neutral conditions (Scheme 2).[20]

Reactions of α-acyloins 3 with (hetero)aromatics

3,3´-Bisindolylmethanes are important indole derivatives that present a wide range of important biological activities.[21] The most common methods for their preparation involve a catalytic Friedel–Crafts reaction of indoles with carbonyl derivatives.[22] In this field, symmetrical 2,2-bis(indol-3-yl)-1-arylethanones‡ have been accessed from the treatment of indoles with arylglyoxals,[23] aryl methyl ketones,[24] and styrenes or α-hydroxyacetophenones.[25] Remarkably, none of the reported methodologies for the synthesis of bis(indol-3-yl)ethanones allowed the access to the corresponding unsymmetrical substrates, i.e. ethanones bearing two different indolyl substituents at the α-position.[26] So, we thought that bis(indolyl)methane derivatives such as **6**, bearing two different indolyl moieties, could be prepared by direct nucleophilic substitution of indolyl α-acyloins **3** with different indoles **4** (Table 1).[27] Under our typical Brønsted acid-catalyzed conditions,[17] PTSA (5 mol%) in acetonitrile at room temperature, the α-acyloins **3a-e** previously prepared reacted efficiently with a selection of indoles **4** affording the corresponding unsymmetrical bis(indolyl)ethanones **6** in high to excellent yields, which were isolated in pure form by simple filtration. Different commercially available indoles **4**, including *N*-methyl substituted (entry 1), *N*-unsubstituted (entries 3 and 12), 1,2-disubstituted (entries 2 and 7), 2-substituted (entries 6, 9 and 10), as well as indoles bearing electron-withdrawing groups (entries 4, 5, 8 and 11), are useful nucleophilic partners for this transformation. This methodology allows the preparation of a variety of unsymmetrical bis(indol-3-yl)carbonyl compounds **6** under mild reaction conditions and in short reaction times, being water the only byproduct of the process. In addition, the scalability of this reaction was demonstrated by the treatment of α-acyloin **3a** with 1,2-



Scheme 2 Reaction of indoles with α-oxoaldehydes. Synthesis of indol-3-yl α-acyloins **3**.

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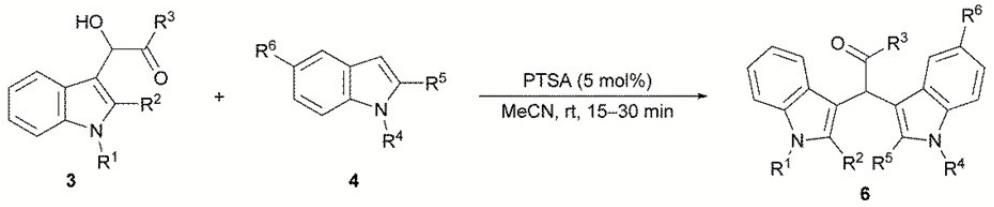
Table 1 Synthesis of unsymmetrical bis(indol-3-yl)ethanones 6

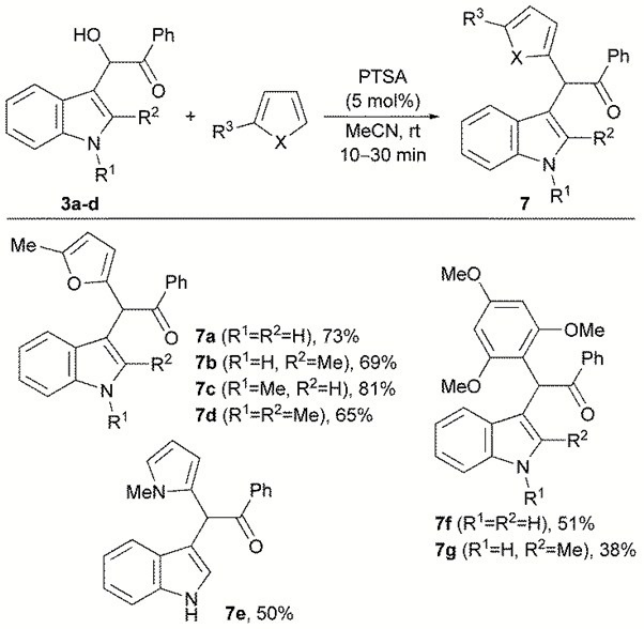


Entry	α-Acyloin	R^1	R^2	R^3	Indole	R^4	R^5	R^6	Product	Yield[a] (%)
1[b]	**3a**	H	H	Ph	**4c**	Me	H	H	**6ac**	92
2	**3a**	H	H	Ph	**4d**	Me	Me	H	**6ad**	86
3	**3b**	H	Me	Ph	**4a**	H	H	H	**6ba**	99
4	**3b**	H	Me	Ph	**4e**	H	H	Br	**6be**	93
5	**3b**	H	Me	Ph	**4f**	H	H	NO_2	**6bf**	91
6	**3c**	Me	H	Ph	**4b**	H	Me	H	**6cb**	90
7	**3c**	Me	H	Ph	**4d**	Me	Me	H	**6cd**	98
8	**3c**	Me	H	Ph	**4f**	H	H	NO_2	**6cf**	90
9	**3c**	Me	H	Ph	**4g**	H	Ph	H	**6cg**	95
10	**3d**	Me	Me	Ph	**4b**	H	Me	H	**6db**	89
11	**3d**	Me	Me	Me	**4e**	H	H	Br	**6de**	85
12	**3e**	Me	H	Me	**4a**	H	H	H	**6ea**	70

[a] Isolated yield based on starting α-acyloin **3**. The final compounds precipitate from the reaction mixture and were isolated by filtration. [b] The reaction mixture was stirred overnight.

dimethylindole on a 5 mmol scale, isolating the corresponding bis(indolyl) acetophenone **6ad** in 85% yield (1.61 g).

Having developed an efficient Brønsted acid-catalyzed protocol for accessing a variety of unsymmetrical bis(indolyl)ethanones, we proceeded to evaluate whether other π-excessive heteroaromatics could participate in this process. We found that treatment of 2-methylfuran with α-acyloins **3** provided the corresponding α-furan-2-yl functionalized α-indol-3-yl ketones **7a-d** in good yields and in short reaction times (Scheme 3). *N*-Methylpyrrole also exhibited good reactivity, although under these conditions the corresponding α-pyrrol-2-yl ketone **7e** was isolated in moderate yield, probably due to the higher reaction time needed for complete consumption of the starting acyloin (Scheme 3). Moreover, other electron-rich aromatic compounds such as phenol, *p*-cresol and 1,3,5-trimethoxybenzene were also tried as potential nucleophiles for acyloins **3**. Whereas the phenol derivatives gave rise to decomposition products, α-indolyl α-(trimethoxyphenyl) ketones **7f,g** could be obtained in moderate yields under PTSA-catalysis (Scheme 3).



Scheme 3 Reaction of **3** with other electron-rich (hetero)aromatic. Synthesis of **7**.

Reactions of α-acyloins 3 with heteroatomic nucleophiles

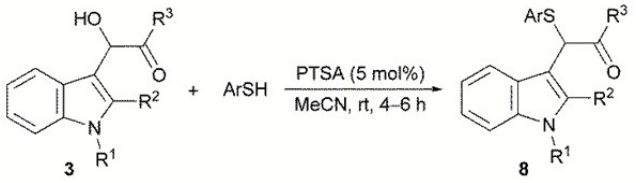
Despite the fact that compounds bearing both sulfur atom and indole frameworks are proven to exhibit biological activity,[28] methods for preparing 3-substituted indoles bearing sulfur-containing groups have been rarely reported[29] and, moreover, no methodologies for the synthesis of α-indol-3-yl-α-thioketones have been described. So, the development of new strategies for accessing this type of compounds with potential

pharmacological activities is highly desirable. Considering that thiols have been used as versatile soft nucleophiles for S_N1-type reactions of activated alcohols,[30] we postulated that they could also react with α-acyloins **3** under Brønsted acid-catalysis.

And so, when a variety of thiophenols was examined as nucleophiles in the S_N1 type reaction of **3** under PTSA-catalysis, α-thioaryl functionalized α-indolyl ketones **8** were obtained in high yields (Table 2). All the tested thiols underwent clean reactions, although in these cases the final compounds did not precipitate and were isolated after extraction of the reaction mixtures. Both electron-withdrawing groups and electron-donating groups on the benzene ring of starting thiophenol, as well as *ortho*-substituents, were well tolerated, allowing the construction of new and interesting α-indolyl-α-thioaryl carbonyl compounds **8** in high yields.

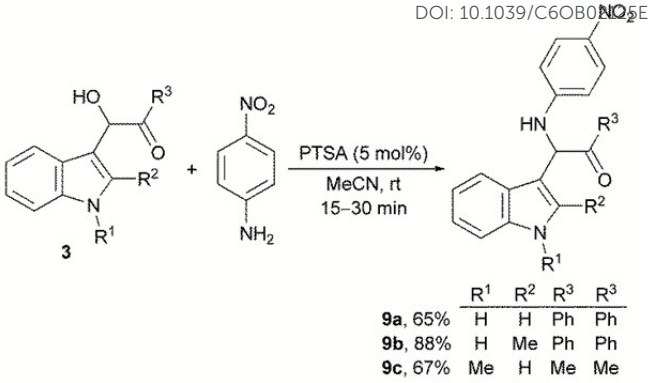
The diversity and applicability of the PTSA-catalyzed nucleophilic substitution for the synthesis of α-functionalized α-indolyl ketones were also surveyed with nitrogenated nucleophiles, such as electron-deficient anilines and sulfonamides. All the attempts carried out using benzenesulfonamide, *p*-choroaniline, or *p*-cyanoaniline were unfruitful leading to decomposition under PTSA-catalysis. Gratifyingly, *p*-nitroaniline efficiently underwent the substitution reaction with selected α-acyloins **3** affording the corresponding α-aminoketones **9** in good yields and in short reaction times, except **9c** that requires overnight stirring (Scheme 4). It should be remarked that whereas different routes have been described for the synthesis of α-amino-α-indolyl esters or amides, (indol-3-yl)glicine derivatives,[31] the preparation of α-amino-α-indolyl ketones has not been well-developed, with few approaches reported in the literature mainly based on the α-arylation of α-amino carbonyl compounds.[32]

Table 2 Acid-catalyzed substitution reactions of **3** with aromatic thiols. Synthesis of **8**



Entry	**3**	R^1	R^2	R^3	Ar	Product	Yield[a] (%)
1	**3a**	H	H	Ph	4-MeC_6H_4	**8a**	87
2	**3a**	H	H	Ph	4-$MeOC_6H_4$	**8b**	83
3	**3a**	H	H	Ph	2,5-$(MeO)_2C_6H_3$	**8c**	76
4	**3a**	H	H	Ph	3,4-$(MeO)_2C_6H_3$	**8d**	75
5	**3b**	H	Me	Ph	2-BrC_6H_4	**8e**	78
6	**3c**	Me	H	Ph	2-BrC_6H_4	**8f**	86
7	**3c**	Me	H	Ph	4-ClC_6H_4	**8g**	89
8	**3c**	Me	H	Ph	4-$MeOC_6H_4$	**8h**	87
9	**3d**	Me	Me	Ph	4-$MeOC_6H_4$	**8i**	75
10	**3e**	Me	H	Me	4-MeC_6H_4	**8j**	73

[a] Isolated yield based on starting α-acyloin **3**.



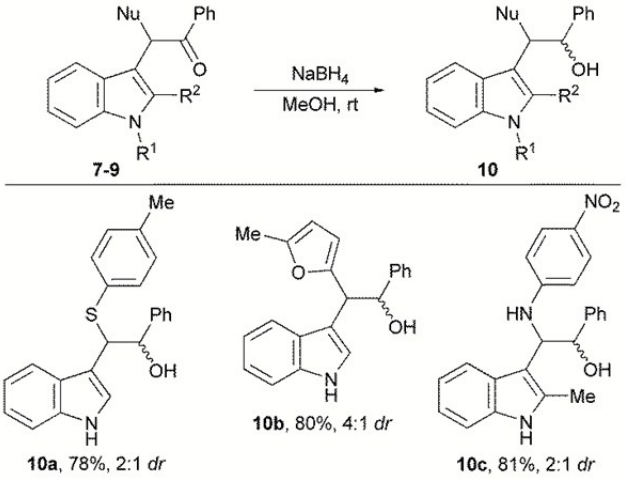
Scheme 4 Reaction of **3** with *p*-nitroaniline. Synthesis of amino derivatives **9**.

Reduction of α-functionalized α-indol-3-yl ketones

As we have mentioned above, tryptophols are important indole derivatives due to their biological activity.[5] One of the most direct access to these compounds is the direct alkylation of indoles with epoxides, where aryl epoxides are cleaved by indoles under acid catalysis with preferential attack at the benzylic position resulting in the formation of primary alcohols.[33] Due to the potential interest of new functionalized tryptophol derivatives, we carried out the reduction of a selection of the previously prepared α-functionalized α-indolyl ketones with $NaBH_4$. In this way, the new tryptophol derivatives **10** were prepared in high yields as a variable mixture of diastereoisomers, although the major diastereoisomer of **10b** and **10c** could be isolated after column chromatography (Scheme 5).[34]

Reactions of α-acyloins 3 with 1,3-dicarbonyl compounds

Taking into account the interest for using other C-centered nucleophiles for creating new C–C bonds in this process, and the fact that the catalytic alkylation of 1,3-dicarbonyls with



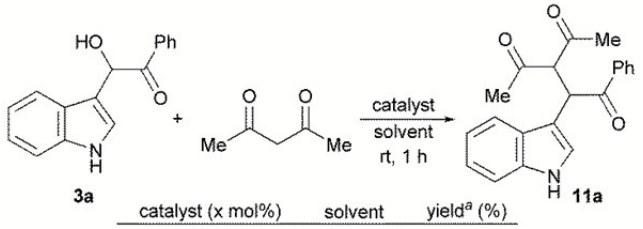
Scheme 5 Synthesis of tryptophol derivatives **10**.

alcohols has become a relevant atom-economical organic process,[35] our studies went on with attempts to evaluate the reactivity of acetylacetone with α-acyloin **3a** to ascertain if the formation of 1,4-dicarbonyl functionalized indole **11a** would be feasible. Unfortunately, the reaction led to decomposition under PTSA-catalysis and so, we examined the proposed experiment using different catalytic systems (Scheme 6). As Brønsted acids, including triflic acid, did not result suitable catalysts for this reaction, we tried different Lewis acids that have been previously used in related alkylations of 1,3-dicarbonyls.[36] After some experiments, gratifyingly, we found that $Cu(OTf)_2$ was able to promote the desired reaction in toluene at room temperature giving rise to **11a** in high yield after 1 h (Scheme 6). The success of this copper species could be based on its dual role for activating both the 1,3-dicarbonyl derivative, by the generation of copper enolate species, and the electrophilic partner, by protonation of the alcohol with the released triflic acid.[37]

Under the optimized conditions ($Cu(OTf)_2$, toluene), we next tested the scope of this reaction regarding the 1,3-dicarbonyl partner (Table 3). Using some of the prepared α-acyloins **3** and representative β-dicarbonyls we were able to prepare a wide variety of tricarbonyl derivatives **11** in usually high yields. Both 1,3-diketones such as acetylacetone (entry 1) and β-keto esters like ethyl acetoacetate and ethyl benzoylacetate (entries 2 and 3) were proven to be viable nucleophiles for reacting with model α-acyloin **3a** affording the corresponding tricarbonyl compounds **11a-c**. Unfortunately, the copper-catalyzed addition of a β-diester (diethyl malonate) was not successful under these reaction conditions leading to decomposition.[38] Other indol-3-yl α-acyloins such as **3b** and **3d** also underwent substitution reactions with β-dicarbonyls leading to the expected alkylated derivatives **11e,f** (entries 4 and 5) in high to excellent yields.

Synthesis of furanyl indoles

It is interesting to note that indoles substituted with aromatic heterocyclic rings, such as furans, at C-3 are highly

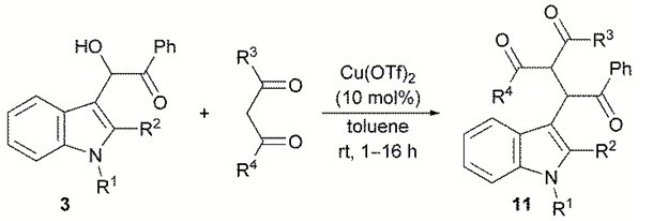


catalyst (x mol%)	solvent	yield[a] (%)
PTSA (5)	MeCN	–
$(PhO)_2P(O)(OH)$ (5)	toluene	–
TfOH (5)	MeCN	–
TfOH (5)	toluene	–
I_2 (10)	toluene	45
$In(OTf)_3$ (5)	toluene	25
$FeCl_3$ (10)	toluene	23
$Sc(OTf)_3$ (10)	toluene	23
$Cu(OTf)_2$ (10)	toluene	83

[a] Determined by ^{1}H NMR with internal standard.

Scheme 6 Reaction of **3a** with acetylacetone. Optimization of the reaction conditions.

Table 3 Reactions of **3** with 1,3-dicarbonyl compounds. Synthesis of tricarbonyl derivatives **11**



Entry	3	R^1	R^2	R^3	R^4	Product	Yield[a] (%)
1	**3a**	H		Me	Me	**11a**	90
2	**3a**	H	H	Me	OEt	**11b**	68
3	**3a**	H	H	Ph	OEt	**11c**	80
4	**3b**	H	Me	Me	Me	**11d**	93
5	**3d**	Me	Me	Me	Me	**11e**	76

[a] Isolated yield based on starting α-acyloin **3**.

interesting compounds displaying a wide range of biological and pharmaceutical activity.[39] However, the access to these compounds is challenging as the most direct route involving direct heteroarylation of indoles suffers from several drawbacks such as the lack of regioselectivity, which is highly dependent on the nitrogen substitution, and the tendency for homocoupling of heteroarenes in the oxidative C–H/C–H cross-coupling between two different heteroarenes.[40] So, methods for preparing biheteroaryl compounds, mainly those bearing two linked electron-rich heterocycles such as indoles and furans, remains very limited and procedures involving indirect heteroarylation, i.e. formation of the second heterocyclic ring from a functionalized indole precursor, predominate in this field.[41] Having in mind that 1,4-dicarbonyl compounds are the usual starting materials for the Paal–Knorr synthesis of furans, we tried to develop a procedure for the one-pot preparation of 3-furyl-substituted indoles. After some experimentation, we found that treatment of **11a** with a stoichiometric amount of PTSA in toluene at 50 ºC for 2 h gave rise to indole-furan conjugate compound **12a** in 85% yield. In addition, taking advantage from the use of the same solvent for the two reactions (the initial alkylation of the β-dicarbonyl and the subsequent furan formation), we decided to perform the synthesis of **12a** as a direct two-step protocol without purification of the tricarbonyl intermediate **11** (Scheme 7). In this way a selection of furan derivatives **12a-d** were prepared in high yields, showing the potential of this strategy for the direct access to highly functionalized 4-(1*H*-indol-3-yl)-3-carbonyl-2,5-disubstituted furans (Scheme 7). In addition, furans **12** could be also prepared by base-mediated cyclization reactions. So, treatment of tricarbonyl derivative **11e** with NaOH in EtOH at room temperature gave rise to furan **12c** in an almost quantitatively yield.

However, when 3-methyl-2,4-pentanedione was used in the reaction with **3a** under copper-catalysis followed by Brønsted acid-promoted cyclization, an unexpected new furan derivative **13**, lacking the acetyl group, was obtained in moderate yield (Scheme 8). Its formation could be understood considering that the initially generated tricarbonyl derivative

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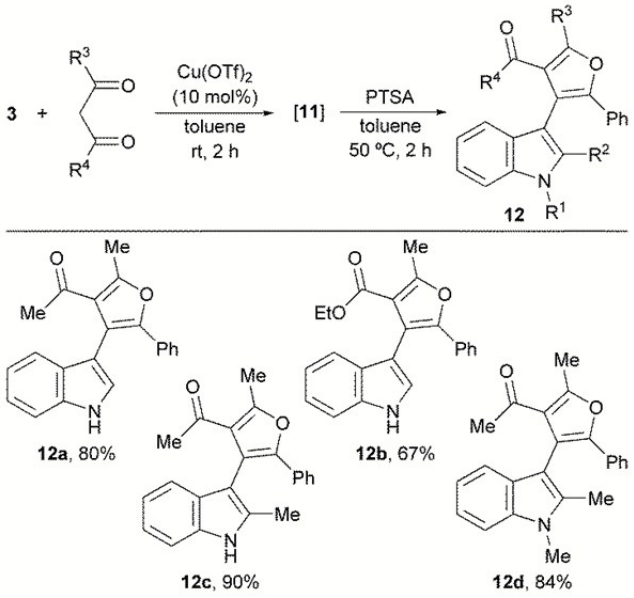
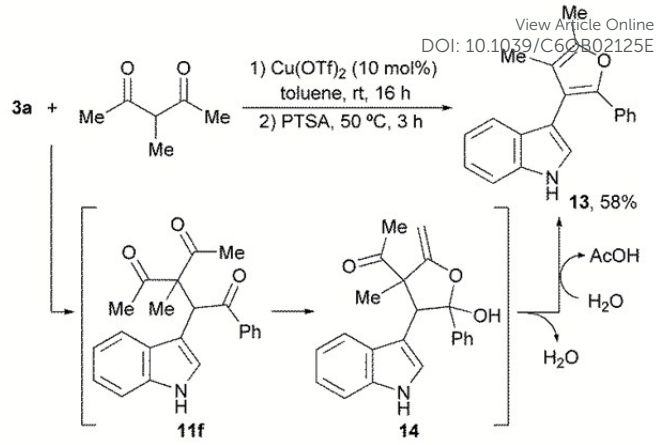


Scheme 7 Reaction of **3** with 1,3-dicarbonyl compounds and further Brønsted acid treatment. Synthesis of furans **12**.



Scheme 8 Reaction of **3a** with 3-methyl-2,4-pentanedione. Synthesis of furan **13**.

11f, bearing a quaternary carbon, undergoes acid-promoted *O*-cyclization leading to **14**. This intermediate evolves by dehydration, a subsequent deacylation and further isomerization of the exocyclic double bond.

Conclusions

In conclusion, we have described the synthesis of a wide variety of α-functionalized α-(indol-3-yl) ketones by the acid-catalyzed direct nucleophilic substitution of readily available indol-3-yl α-acyloins, which have been shown for the first time as useful alkylating reagents for direct S_N reactions under acid–catalysis. This methodology complements previously described ones based on the use of arylsulfonylalkyl indoles, providing a straightforward access to indole derivatives with potential biological activity. This strategy features mild reaction conditions, broad nucleophile scope as well as high yields. The synthetic utility of some of the obtained compounds has been outlined by the preparation of C3-furanyl functionalized indole derivatives.

Experimental section

General procedure for the synthesis of α-(indol-3-yl) carbonyl compounds 6-9

PTSA (5 mol%, 9 mg) was added to a solution of the corresponding α-acyloin **3** (1 mmol) and nucleophile (1 mmol for the synthesis of **6-8**, 1.1 mmol of *p*-nitroaniline for the synthesis of **9**) in MeCN (2 mL). The resulting reaction mixture was stirred until the final product precipitates or the starting acyloin was consumed as determined by TLC (0.25–16 h). In the first case, the precipitated product was isolated in pure form by simple filtration, whereas in the last case, the crude mixture was quenched with aqueous NaOH (0.5 M) and extracted with DCM (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated at reduced pressure. The residue was purified by flash chromatography using mixtures of hexane and EtOAc as eluents to obtain the corresponding α-(indol-3-yl) carbonyl compounds derivatives **6-9** in the yields reported in Tables 1-2 or Schemes 3-4.

Acknowledgements

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Notes and references

‡ A particular example for the synthesis of 1,1-bis(indol-3-yl)acetone has been reported by the reaction of indole with 1,3-dichloroacetone. See ref 9c.

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