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A novel synthesis of *N*-hydroxy-3-aroylindoles and 3-aroylindoles†

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A straightforward indole synthesis *via* annulation of *C*-nitrosoaromatics with conjugated terminal alkynones was realised achieving a simple, highly regioselective, atom- and step economical access to 3-aroylindoles in moderate to good yields. Further functionalizations of indole scaffolds were investigated and an easy way to JWH-018, a synthetic cannabinoid, was achieved.

Indole compounds are deeply studied because of their biological activity and continue to capture the attention of synthetic organic chemists (Figure 1). A large number of original indole ring syntheses and applications of known methods to new problems in indole chemistry have been reported so far.[1] Our general interest in the chemistry of indoles led us to introduce in the last years a synthetic approach to the formation of the indole ring by cycloaddition of nitro- and nitrosoarenes with alkynes.[2] Indoles, *N*-hydroxy- and *N*-alkoxyindoles were regioselectively produced in moderate to good yields. Ragaini's research groups reported a very efficient Pd-based catalyzed reaction with similar regioselectivities and high turn-over parameters using nitroaromatics as starting materials.[3] Recently Srivastava and coworkers developed a gold-[4a] and a copper-catalyzed[4b] analogue annulation affording indoles by reaction of nitrosoarenes with aromatic alkynes. Naturally occurring marine alkaloids like meridianins, commonly known as kinase inhibitors, were prepared through the annulation of nitrosoarenes with substituted ethynylpyrimidines.[5] Efficient synthetic protocols starting from arylhydroxylamines were introduced by some of us using the *in situ* generation of nitrosoaromatics by oxidation with Fe(Pc)(Iron phthalocyanines).[6]

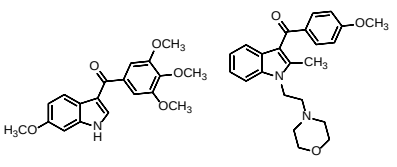

Figure 1 Synthetic bioactive indole compounds

The ever growing interest in *N*-hydroxyindole derivatives was recently illustrated by the biological activities reported for some of these compounds that became interesting candidates in different therapies and as anti-cancer agents.[7] The 1-hydroxyindole nucleus was recently found in pigments from flower pot parasol *Leucocoprinus birnbaumii*[8] and has received ever growing attention by many research groups for its role in bioactive molecules.[9] The *N*-hydroxyindole unit, or of an analogue indoline nitrone, is a fundamental fragment of very interesting naturally occurring compounds such as nocathiacin I,[10] coproverdine[11] and stephacidin B, a highly complex dimeric prenylated *N*-hydroxyindole alkaloid that contains 15 rings and 9 stereogenic centers and exhibits potent activity against prostate carcinoma;[12] the corresponding monomeric compound, avrainvillamide was recently afforded by two different total syntheses by Myers[13a] and Baran[13b] and displayed antibiotic activity towards several Gram positive cocci.[14] Stability of *N*-hydroxyindoles has been a source of debate where they are frequently cited as unstable and elusive compounds that can be reduced to indoles or stabilized through alkylation or acylation to avoid their decomposition or dimerization.[15] Most of the syntheses of *N*-hydroxy- and *N*-alkoxyindoles reported in literature employ an intramolecular approach to the indole ring closure.[16] Previous intramolecular synthetic approaches to *N*-hydroxyindoles were reported by different research groups starting from nitrostilbenes[17] and a theoretical study by Davies and Houk discussed the formation of *N*-hydroxyheterocycles during the deoxygenation of nitroaromatics.[18] A recent interesting work by Liu, Zhou et al. reported the synthesis of *N*-hydroxyindoles by Rh(III)-catalyzed C-H cyclization of arylnitrones and diazo compounds.[19]

3-Acylindoles are known to be bioactive compounds and recent studies highlighted their interesting properties and various synthetic approaches.[20] Some synthetic compounds such as BPR0L075 (6-methoxy-3-(3',4',5'-trimethoxy-benzoyl)-1*H*-indole) showing 3-aroylindole unit were discovered to be potent antitubulin agents.[21] 3-Aroylindoles were differently prepared by classic synthetic approaches by acylation of preformed indole substrates[22a-c] and very recently by Pd,[22d-e] Pd-Cu,[22f] Cu[22g] and acid catalyzed[22h] reactions. Not many indolization procedures are known to afford directly 3-acylindoles starting from easily available reactants.[23]

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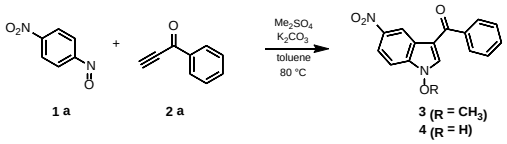

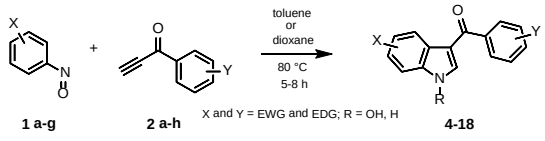

Table 1 Survey for the optimization of the reaction conditions[a]

Entry	Alkynone/nitrosoarene molar ratio	Alkylative agent / base	R	Prod.	Yield (%)
1	15/1	Me_2SO_4 / K_2CO_3	CH_3	**3**	traces[b]
2	5/1	Me_2SO_4 / K_2CO_3	CH_3	**3**	traces[b]
3	15/1	none	H	**4**	35[c]
4	12/1	none	H	**4**	38[c]
5	10/1	none	H	**4**	40[c]
6	5/1	none	H	**4**	42[c]
7	1/1	none	H	**4**	53[c]

[a] All reactions were carried out using **1a** and **2a** in toluene for 5h; [b] product isolated by chromatography; [c] product precipitated

Thus stimulated by the intention to apply our convergent indole synthetic approach to the one-pot preparation of highly functionalizable compounds and/or biologically active products having the 3-aroylindole fragment, we used 1-phenyl-prop-2-yne-1-one **2a** as the simplest starting material for a wide survey with nitrosoaromatic derivatives as reaction partners. Previous studies revealed that *C*-nitrosoaromatics with electron withdrawing groups show generally faster reaction times and better product yields. The study for the optimization of the reaction conditions was carried out using 4-nitronitrosobenzene **1a** and 1-phenyl-2-propyne-1-one **2a** (Table 1). A general drawback for our previous annulation reactions between nitrosoarenes and alkynes was the large excess of alkynes (10-15 fold) that was always used.

Envisioning an instability of the *N*-hydroxyindoles our first nitroso-alkyne cycloaddition reactions between 4-nitro-nitrosobenzene **1a** and 1-phenyl-prop-2-yn-1-one **2a** were run under alkylating conditions (K_2CO_3 and Me_2SO_4 both 6 fold), but this strategy was not fruitful and led us to isolate the corresponding *N*-methoxy-3-aroylindole only in traces. To our delight, working in the absence of dimethyl sulphate and potassium carbonate, a solid precipitated in the reaction mixture. After spectroscopic characterization, it was identified as composed only by *N*-hydroxy-5-nitro-3-benzoylindole and it was isolated simply by filtration without any other further purification.

We then determined whether such a large excess of alkyne was strictly necessary to get efficient conversion of nitrosoarenes to target indoles avoiding the degradation to azoxy-derivatives, generally the most relevant side products observed in the cycloaddition of nitrosoarenes with arylacetylenes. Seeking to optimize the reaction conditions we used different molar ratios nitrosoarene/alkynone, (e.g. 1:5, 1:12, 1:15), but surprisingly, we found comparable or better yields of indole products by performing the reactions with a 1:1 nitrosoarene/alkynone molar ratio (Table 1). In contrast to the *N*-hydroxy-3-arylindoles, *N*-hydroxy-3-aroylindoles are generally more stable and do not undergo dimerization to kabutanes[15a,24] under the standard reaction conditions. The procedures were highly functional group tolerant. Using conjugated alkynones as starting materials the reaction proceeds with the regioselective formation of *N*-hydroxy-3-aroylindoles and/or 3-aroylindoles (Table 2).

Table 2 Nitrosoarene-alkynone cycloaddition reactions [a]

Entry	ArNO	X	ArC(O)C≡CH	Y	R	Prod.	Yield (%)
1	**1a**	4-NO_2	**2a**	H	OH	**4**	54 [b, c]
2	**1a**	4-NO_2	**2b**	2-Cl	OH	**5**	70 [b, c]
3	**1a**	4-NO_2	**2c**	2-Br	OH	**6**	52 [b, c]
4	**1a**	4-NO_2	**2d**	3-NO_2	OH	**7**	69 [b, c]
5	**1a**	4-NO_2	**2e**	4-NO_2	OH	**8**	62 [c]
6	**1a**	4-NO_2	**2f**	4-OCH_3	OH	**9**	37 [b, c]
7	**1a**	4-NO_2	**2g**	4-CHO	OH	**10**	31[c]
8	**1a**	4-NO_2	**2h**	3,4-OCH_2O	OH	**11**	61 [c]
9	**1b**	4-COOH	**2b**	2-Cl	OH	**12**	69 [c, d, e]
10	**1b**	4-COOH	**2f**	4-NO_2	OH	**13**	67 [c, d, e]
11	**1c**	H	**2a**	H	H	**14**	25 [f]
12	**1d**	4-COOEt	**2a**	H	H	**15**	27 [f]
13	**1e**	4-CH_3	**2a**	H	H	**16**	20 [f]
14	**1f**	4-OCH_3	**2a**	H	H	**17**	30 [f]
15	**1g**	2-COOMe	**2a**	H	OH	**18**	33 [f]

[a] All reactions were carried out using ArNO (1 mmol) and ArC(=O)C≡CH (1 mmol) in 12 ml of toluene; [b] this reaction was carried out even using a large excess of alkyne but no better yields were collected and only faster reaction times were registered; [c] product precipitated; [d] reaction carried out in dioxane; [e] product recrystalyzed; [f] product isolated by chromatography;

This process shows an excellent atom and step economy. A wide substrate scope was explored using different substituted nitrosoarenes and arylalkynones affording indole compounds in moderate to excellent yields (Table 2). Only 3-substituted regioisomers were isolated. Procedures carried out with electron-deficient nitrosoaromatics registered better product yields and shorter reaction times. Electron-rich nitrosoarenes show the prevalent formation of indoles instead of *N*-hydroxyindoles. Minor conversions and moderate yields were observed by using nitrosoaromatics with electron donating groups. With a few nitrosoarenes, N-H indoles were detected as minor products. A plausible explanation could be an internal redox process in which a relevant role is played by the electronic properties of both reagents. The mechanism of an analogous annulation was studied some years ago using terminal arylacetylenes[2e] instead of aroylacetylenes. We reported that the reaction probably occurs through a stepwise diradical cycloaddition with rate-limiting N-C bond formation and rapid C-C connection to form the *N*-hydroxyindole product. Further studies employing electrochemical methods will be carried out in the near future to investigate other aspects of the reaction mechanism like the reduction of *N*-hydroxyindole compounds to N-H indole products observed in some cases. Interestingly, running the reaction with pentafluoro-nitrosobenzene, no cycloaddition products were detected, proving the necessity of an unsubstituted carbon *ortho*- to the nitroso group. The electronic properties of substituents on the ring of the aromatic ynone does not seem to play a dramatic role neither in product yields nor for reaction times.

To confirm the surmised 3-regioselectivity of the reaction, a single crystal of *N*-hydroxy-3-(2'-chlorobenzoyl)-5-nitro-1*H*-indole (compound **5**) was obtained and its X-ray structure[§] is reported in Figure 2. No traces of the 2-substituted regioisomers were detected in the reaction mixtures.

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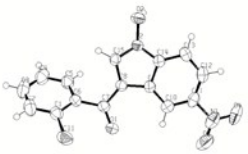
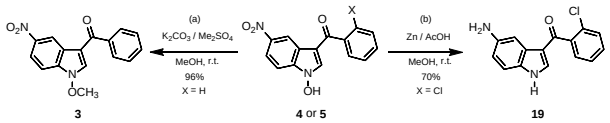


Figure 2 X-ray derived molecular structure of compound **5**, with partial labelling scheme. Thermal ellipsoids are drawn at the 50% level.

The versatility of the indole products was tested in functionalization procedures using compounds **4** and **5** as starting materials (Scheme 1).



Scheme 1 Functionalization reactions of compound **4** and **5**

Compound **4** was methylated by reaction with dimethyl sulphate in the presence of K_2CO_3 as base in MeOH affording the corresponding *N*-methoxyindole derivative **3** in 96% yield (path (a)). In a poorly selective reductive reaction compound **5** was heated with Zn/AcOH and performing contemporarily the reduction of the nitro group and the N-OH bond to N-H group affording **19** in 70% yield (path (b)).

With the aim to generalize the application of the cycloaddition between nitrosoarenes and alkynones, ethynyl ketones containing heterocyclic frameworks or other conjugated units, organometallic moieties and polycyclic fragments were tested and an extension of the synthetic scope of the reaction was achieved (Table 3). Indole derivatives **21-24** (Table 2 entries 1-4) showing the benzotriazole (Bt) unit were prepared by cycloaddition of nitrosoaromatic compounds **1 a-c, h** with 1-(1*H*-1,2,3-benzotriazol-1-yl)-2-propyn-1-one **20a**.[25] Tremendous progress has been achieved in the field of benzotriazole chemistry and different major functions of benzotriazole in organic transformations were excellently illustrated very recently by Katritzky and coworkers focusing the activity of Bt as leaving group, proton activator, cation stabilizer, anion and radical precursor.[26] The use of Bt (benzotriazole) as leaving group is a powerful tool to achieve a wide class of indole derivatives showing biological activities. Compounds **21-24** are good candidates to be furtherly functionalized to many different indole alkaloid products. The potential value of this transformation is currently in progress and will be deeply investigated in the near future.

4-Nitronitrosobenzene **1a** and 4-nitrosobenzoic acid **1b** proved to be superior reagents with the alkynones through stoichiometric reaction in toluene or dioxane at 80 °C. *N*-Hydroxyindoles bearing a nitro group at C-5 always precipitated from the reaction mixture and were isolated by filtration. The same thing was observed for *N*-hydroxyindoles bearing a COOH group at C-5, but because 4-nitrosobenzoic acid was scarcely soluble in the common solvents, dioxane was used for cycloadditions. 3-Aroyl-1-hydroxy-1*H*-indole-5-carboxylic acids were extremely insoluble and precipitated as yellow solids as the reaction proceeded, together with azoxybenzene-4,4'-dicarboxylic acid. Removal of this by-product was sometimes achieved by recrystallization from dichloromethane or ethyl acetate.

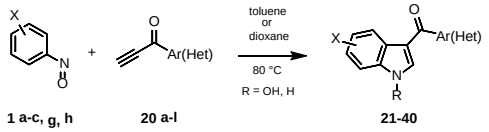
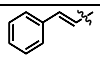
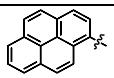
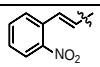


Table 3 Nitrosoarene-alkyne cycloadditions with other carbonyl-conjugated ynones[a]

Entry	ArNO	X	ArC(O)C≡CH or HetC(O)C≡CH	Ar or Het	R	Prod.	Yield (%)
1	**1a**	4-NO_2	**20a**		OH	**21**	57 [b, c]
2	**1b**	4-COOH	**20a**		OH	**22**	68 [b, d]
3	**1h**	4-CN	**20a**		OH	**23**	40 [b]
4	**1c**	H	**20a**		OH	**24**	40 [b]
5	**1a**	4-NO_2	**20b**		OH	**25**	47 [b, e]
6	**1a**	NO_2	**20c**		OH	**26**	20 [b]
7	**1g**	2-COOMe	**20c**		H	**27**	30 [f]
8	**1a**	4-NO_2	**20d**		OH	**28**	65 [a, e]
9	**1a**	4-NO_2	**20e**		OH	**29**	50 [b]
10	**1a**	4-NO_2	**20f**		OH	**30**	51 [b]
11	**1a**	4-NO_2	**20g**		OH	**31**	65 [b]
12	**1a**	4-NO_2	**20h**		OH	**32**	36 [b]
13	**1h**	4-CN	**20h**		OH	**33**	29 [b]
14	**1a**	4-NO_2	**20i**		H	**34**	49 [b]
15	**1a**	4-NO_2	**20j**		OH	**35**	68 [b]
16	**1h**	4-CN	**20j**		OH	**36**	30 [b]
17	**1c**	H	**20j**		OH	**37**	38 [f]
18	**1c**	H	**20j**		H	**38**	17 [f]
19	**1h**	4-CN	**20k**		OH	**39**	33 [b]
20	**1a**	4-NO_2	**20l**		OH	**40**	27 [b]

[a] All reactions were carried out using ArNO (1 mmol) and Ar(Het)C(=O)C≡CH (1 mmol) in 12 ml of toluene; [b] product precipitated; [c] reaction carried out on gram scale; [d] reaction carried out in dioxane; [e] this reaction was carried out even using a large excess of alkyne but no better yields were collected and only faster reaction times were registered; [f] product isolated by chromatography.

The product **39** (Entry 19, Table 3) was furtherly investigated because this very versatile substrate can be used for two different annulations in the aim to afford biindole scaffolds and quinoline products (path (a) and (b), Scheme 2). Indolization was achieved in 25% yield, via a cyclization in a Cadogan-Sundberg type procedure using PPh_3 under microwave irradiation. The quinoline derivative was synthesized by reaction of compound **39** with indium and ammonium chloride at reflux in methanol/water (24% yield).

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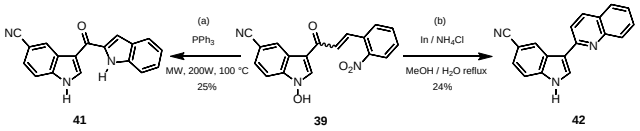
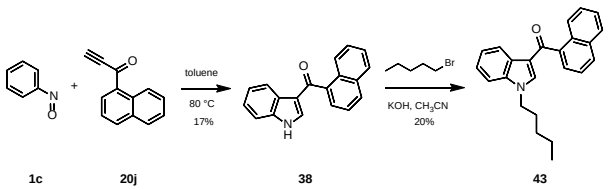


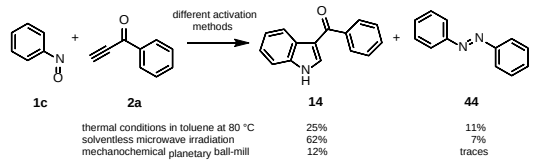
Scheme 2 Further functionalizations and transformations of **39**

As cited before some 3-aroylindoles are known as antinociceptive drugs and cannabinoid agonists and NSAID (Non Steroidal Anti-Inflammatory Drugs).[27]



Scheme 3 Alternative synthesis of JWH-018

Pravadoline is a quite simple and small molecule known as an analgesic drug.[28] Recently a moderate affinity of pravadoline for the cannabinoid receptors was detected. This finding initiated a search for other Amino Alkyl Indoles (AAIs) with higher potency and selectivity in antinociceptive activity. The aminoalkylindoles, naphthalene analogs of pravadoline, have been shown to exhibit cannabinoid agonist activities such as antinociception in animals, inhibition of adenylate cyclase in brain membranes and have high affinity for both the cannabinoid CB1 and CB2 receptors in the brain.[29] Huffman's research group synthesized a huge number of compounds and JWH-018 **43** is only one example that shows a relevant activity as an analgesic chemical from the naphthoylindole family that acts as a full agonist at both the CB1 and CB2 cannabinoid receptors, with some selectivity for CB2.[30] We easily accessed to naphthoylindole scaffolds using different nitrosoarenes in cycloaddition reactions with 1-(naphthalene-1-yl)prop-2-yn-1-one **20j** (Table 3 entries 15-18). With the synthetic technique presented here in our hands, it was intriguing to develop an alternative synthesis for the preparation of bioactive 3-aroylindoles. JWH-018 was synthesized in an interesting shortcut using an alkylative procedure on compound **37** after the cyclization.



Scheme 4 Synthesis of compound **14** with different activation methods

In an explorative study we planned to search a more environmental benign approach to the indolization of nitrosoarenes with alkynones using even different techniques like ball-milling and microwaves in solventless conditions. The product yields were detected by GC analyses. As a model reaction we used nitrosobenzene **1c** and 1-phenyl-2-propyn-1-one **2a** as privileged substrates. Nitrosobenzene, the substrate of choice because it is commercially available and more electron rich than compound **1a**, gave in standard conditions only moderate yields of indole (25%, entry 11, Table 2). Poor yields were also achieved using mechanochemical activation in a planetary ball-mill (12% of indole compound **14** and traces of azo derivative **44**) with large amount of starting materials. An interesting improvement was observed when the reaction was carried out solventless under microwave irradiation (62% of **14** and 7% of **44**) (Scheme 4). This last result prompts further studies for the formation of indole derivatives with unconventional methods.

Conclusions

The necessity to have an efficient and easily available protocol for the preparation of *N*-hydroxyindoles led us to study a direct, effective and atom economical synthesis. In conclusion we developed and reported here a direct methodology for the regioselective preparation of stable *N*-hydroxy-3-aroylindoles and 3-aroylindoles by cycloaddition of nitrosoarenes with conjugated alkynones. Terminal ynones were used for the first time in this kind of reaction and revealed to be privileged reactants for a new regioselective and atom economical indolization procedure. Indoles produced by this protocol are interesting scaffolds for the preparation of high valuable compounds generally known as antinociceptive and NSAID bioactive molecules. Some preliminary reactions using internal alkynones gave poor yields of indole products at the moment, however further optimization of the reaction conditions are under development.

Some of the reactions explored in this research can be easily used as propitious tests to recognize conjugated alkynones through the formation of precipitates by reaction with 4-nitronitrosobenzene. A detailed mechanistic study is in progress. Future developments trying to understand the formation of N-OH indoles and N-H indoles will be carried out by using some voltammetry studies and other electrochemistry technique to disclose the redox step that occurs in some reactions.

Dedication

In Loving Memory of our Friend and Colleague Andrea Dallari

Conflict of Interests

There are no conflicts of interest to declare.

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Notes and references

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† Electronic Supplementary Information (ESI) available: X-ray crystal structure of **5**;details of experimental procedures and spectroscopic data are available and are reported in ESI. For ESI and crystalographic data in CIF or other electronic format see DOI: 10.1039/b000000x/

‡ *Preparative reactions*: Alkynols were prepared through the addition of Grignard reagent (ethynylmagnesium bromide ≡-MgBr) or ethynyltrimethylsilane (≡-$SiMe_3$) in the presence of BuLi to the corresponding arylaldehydes. Eventual cleavage of TMS group is operated by TBAF. Ynones were synthesized by oxidation of the alkynols by Dess-Martin periodinane, MnO_2 or Jones reagent. Nitrosoarenes were prepared by oxidation of the corresponding anilines.

Representative experimental procedure: Nitrosoarene (1 mmol) and alkynone (1 mmol) were combined in toluene (or 1,4-dioxane) under inert atmosphere and heated at 80 °C untill the complete conversion of the reactants (monitoring by TLC). Products were isolated by filtration or chromatography. Detailed procedures are reported in the ESI.

§ Crystallographic data: **5**, $C_{15}H_9ClN_2O_4$, M = 316.69, Monoclinic, *a* = 12.899(2), *b* = 7.780(2), *c* = 13.924(1) Å, β = 94.602(9)°, U = 1392.8(4) $Å^3$, T =298(2) K, space group $P2_1/c$, Z = 4, 2529 unique reflections measured, which were used in all calculations. The final R1 was 0.038 ($I>2\sigma(I)$) and wR(F^2) was 0.095 (all data). CCDC 834062.

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