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Further Developments on the Regioselective Synthesis of 3-Aroylindole Derivatives from *C*-Nitrosoaromatics and Alkynones: A Novel Synthetic Approach to Pravadoline, JWH-073, Indothiazinone Analogues and Related Compounds

Luca Scapinello[1], Federico Vavassori[1], Gabriella Ieronimo[1], Keshav L. Ameta[2*], Giancarlo Cravotto[3], Marco Simonetti[4], Stefano Tollari[1], Giovanni Palmisano[1], Kenneth M. Nicholas[5], Andrea Penoni[1*], Angelo Maspero[1]

[1]Department of Science and High Technology, University of Insubria, Como, Italy
[2]Department of Chemistry, Sardar Patel University, Vallabh Vidyanagar, India
[3]Department of Drug Science and Technology, University of Turin, Turin, Italy
[4]School of Chemistry, University of Manchester, Manchester, UK
[5]Stephenson Life Sciences Research Center, Department of Chemistry and Biochemistry, University of Oklahoma, Norman, OK, USA
Email: *klameta77@hotmail.com, *andrea.penoni@uninsubria.it

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Abstract

An uncatalyzed and easily accessible synthetic approach for the preparation of 3-aroylindoles was investigated using nitrosoarenes and aromatic terminal ethynyl ketones. Indole derivatives were produced in good yields and excellent regioselectivity. Functionalizations of the indole products were carried out affording highly valuable and versatile compounds. The indolization protocol was studied as a fundamental step for the preparation of pravadoline and 1-butyl-3-(1-naphthoyl)indole (JWH-073), bioactive molecules showing antinociceptic properties.

Keywords

Nitrosoarenes, Alkynones, Indoles, Cycoaddition, Annulation

1. Introduction

Conjugated alkynones are generally known as an extremely useful and flexible class of organic compounds [1] [2] [3] [4] that can be used in a multiplicity of

reactions giving a deep variety of derivatives [5] [6] [7]. Their role as Michael acceptors was investigated and recently reviewed by different research groups [8] [9] [10] [11]. Although the feasibility to build heterocycles using conjugated carbonyl derivatives is well-known, a particular class of heterocyclic compounds accessed via chalcones and alkynones can also show biological activity [12]-[17]. In the last decades, nitroso(hetero)arenes have emerged as valuable precursors for the synthesis of heterocyclic rings [18] [19] [20]. Indole, which was nicely referred to as "*The Lord of the Rings*" [21] [22] [23], and indole derivatives are among the most developed and studied heterocycles found in nature. Research groups from both academia and industry introduced innovative synthetic approaches to achieve indolization [24]-[31], which are documented in numerous reviews and books [32]-[37]. Indole compounds have always received deep consideration for their relevant role in medicinal chemistry [38]-[43]. Particularly, 3-aroylindole derivatives [44] [45] [46] have attracted great attention due to their potential bioactivity (**Figure 1**), which has consequently propelled the introduction of novel synthetic routes in recent years [47] [48] [49] [50] [51].

2. Results and Discussion

Synthesis of Indole Compounds by Cycloaddition of Nitrosoaromatics with Alkynones

Our previous studies have led to the development of an innovative strategy for accessing the indole skeleton via cycloaddition of *C*-nitrosoaromatics with alkynes, starting from nitrosoarenes and conjugated aromatic alkynes [52] [53] [54] [55] [56]. By these method indoles, *N*-hydroxyindoles and *N*-alkoxyindoles are produced in moderate to good yields in a very atom-economical fashion. A major drawback of our procedure was the requirement of a stoichiometric excess of the alkyne coupling partner. However, when investigating ethynylpyrimidines for the synthesis of meridianins and related compounds [57], which are known as kinase inhibitors [58], an equimolar ratio between the nitrosoarene and the alkyne could be used.

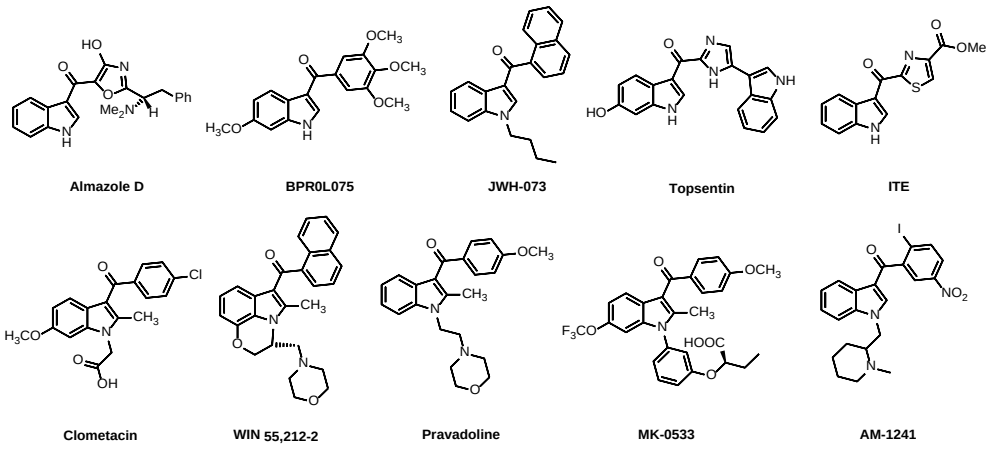


Figure 1. Synthetic and natural bioactive 3-(hetero)aroylindole compounds.

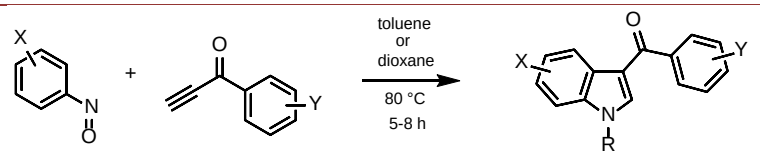
In our more recent work describing the synthesis of 3-aroylindoles with conjugated alkynones and nitrosoarenes, the optimal 1:1 stoichiometric ratio between the two coupling partners was also achieved [59] [60] [61]. Thus, the use of conjugated alkynones instead of simple aromatic alkynes has dramatically improved our indolization strategy. Alkynones can be easily prepared by oxidation of the corresponding alkynols, which, in turn, are obtained from aromatic aldehydes and ethynylmagnesium bromide. *C*-Nitrosoaromatics are instead easily accessible *via* oxidation of the corresponding anilines with different oxidizing agents (Oxone® [62], Na_2WO_4-H_2O_2 [63], $Mo(O)_2(acac)$-H_2O_2 [64], Selenium derivatives [65]).

Herein, we report a more comprehensive investigation of the substrate scope with respect to both nitrosoarenes and (hetero)arylalkynones coupling partners for our recently disclosed strategy for accessing (*N*-hydroxy)-3-aroylindole derivatives. Moreover, the synthethic versatility of some targeted compounds deriving from our indolization method was also demonstrated by their consequent functionalisation, achieving valuable molecular diversity.

In **Table 1**, novel combinations of nitrosoarenes and conjugated arylalkynones were investigated, affording *N*-hydroxy-3-aroylindole compounds and, in some cases, simple 3-aroylindoles. Although the reason behind N–OH/N–H selectivity is still under investigation in our laboratories, while nitrosoarenes that bear highly electron-withdrawing (EWG) groups preferentially yield *N*-OH-3-aroylindoles (entries 1-6, 13), nitrosoarenes with moderately EW substituents or EDGs afford either mixtures of N–OH and N–H compounds (entries 8, 10, 12) or selectively 3-aroylindoles (entries 7, 9, 11). To the best of our knowledge, this single-step procedure represents a synthetic shortcut to generate 3-aroylindoles via the simultaneous formation of new C–N and C–C bonds.

Exploring different alkynone substrates **19a - k** to broaden the scope of the reaction, we then used heteroarenes and other arenes with terminal alkynyl ketone motifs and fragments. Indole derivatives were produced regioselectively and in moderate to good yields (**Table 2**). The structure of the indole products was determined by spectroscopic data. Recently, a X-ray characterization led us to determine the regioselectivity of the reaction and results were detected here by analogy [60]. The indole compounds were collected as the major products, together with the azoxyarene by-products that originate from the reductive dimerization of nitrosoarenes [66]. Most of the products of this substrate scope survey show promise to be further functionalized. Our future and next study will be to employ the annulation of nitrosoarenes with alkynones for the total synthesis of high valuable compounds, natural products, and interesting frameworks with potential bioactivity. Compounds that are formed by the reactions of alkynones with 4-nitronitrosobenzene and other electron-poor *C*-nitrosoaromatics generally precipitated from the reaction mixture affording *N*-hydroxyindoles as major products [61]. Pictures and photos of used reactants and afforded products are reported in **Supplementary Materials**.

Table 1. Nitrosoarene-alkynone cycloaddition reactions.



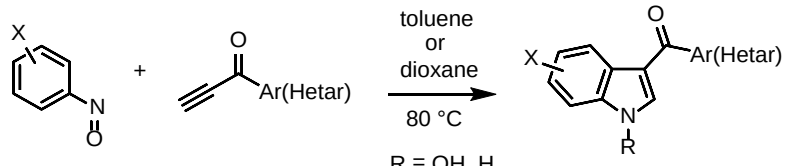
1 a-h **2 a-e** X and Y = EWG and EDG; R = OH, H **3-18** (15-84%)

Entry[a]	ArN=O	X	ArC(O)C≡CH	Y	R	Prod.	Yield (%)
1	**1a**	4-NO_2	**2a**	H	OH	**3**	54[b,c]
2	**1a**	4-NO_2	**2b**	2-Br	OH	**4**	52[b,c]
3	**1a**	4-NO_2	**2c**	2-I	OH	**5**	37[b,c]
4	**1b**	4-COOH	**2a**	H	OH	**6**	62[c,d,e]
5	**1b**	4-COOH	**2b**	2-Br	OH	**7**	50[d,f]
6	**1b**	4-COOH	**2d**	3-NO_2	OH	**8**	84[c,d]
7	**1c**	4-CN	**2a**	H	H	**9**	41[f]
8	**1d**	4-Br	**2a**	H	OH	**10**	15[f]
	1d	4-Br	**2a**	H	H	**11**	35[f]
9	**1e**	4-CF_3	**2a**	H	H	**12**	33[f]
10	**1f**	4-Cl	**2a**	H	OH	**13**	15[f]
	1f	4-Cl	**2a**	H	H	**14**	36[f]
11	**1a**	4-NO_2	**2e**	2-NO_2	H	**15**	48[e,f]
12	**1g**	4-CH_3	**2a**	H	OH	**16**	23[f]
	1g	4-CH_3	**2a**	H	H	**17**	15[f]
13	**1h**	2-NO_2	**2a**	H	OH	**18**	46[f]

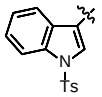
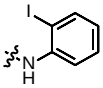
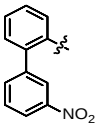
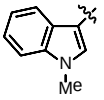
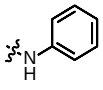
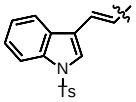
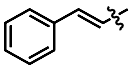
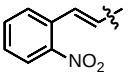
[a]All the reactions, unless otherwise specified, were carried out using ArN=O (1 mmol) and ArC(=O)C≡CH (1 mmol) in 10 - 15 ml of toluene; [b]this reaction was carried out even using a large excess of alkyne but no better yields were collected and only faster reaction times were registered; [c]product precipitated; [d]reaction carried out in dioxane; [e]product recrystallised; [f]product isolated by chromatography.

In the meantime, searching the literature for novel bioactive compounds containing the 3-aroylindole or the 3-heteroaroylindole fragment, indothiazinone (5-nitro-1*H*-indol-3-yl(1,3-thiazol-2-yl)methanone) **38** and related derivatives were targeted [67] [68]. The study of indothiazinone could lead to the development of potential new pharmaceutical agents. Very recent reports described the antibiotic properties of indothiazinone derivatives [69]. Using the synthetic approach described so far, we tried to prepare an indothiazinone related compound. The first step was the synthesis of the corresponding alkynone. The preparation of this compound is particularly challenging because of some partial thermal decomposition of the thiazolinone **19k** previously reported in literature [70] [71] [72] [73]. The formation of an elusive product with the structure of compound **38** was reported (see **Supplementary Materials**).

Table 2. Synthesis of different 3-aroylindoles and 3-heteroaroylindoles.



1 a-d, i-j **19 a-k** **20-38** (15-64%)

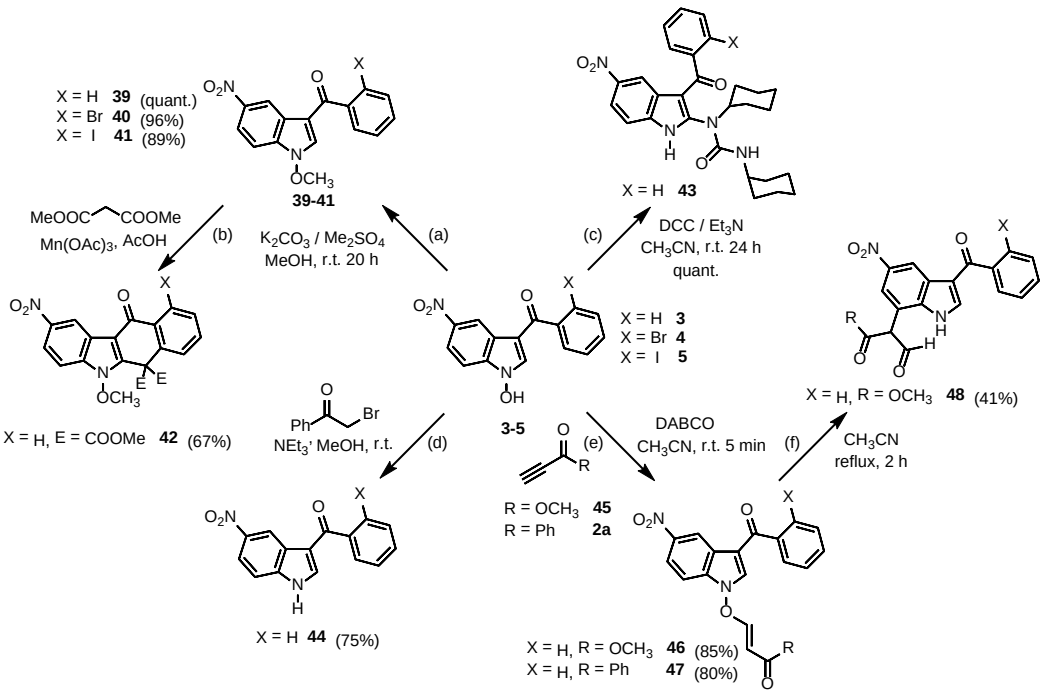
Entry[a]	ArN=O	X	Ar-C(O)C≡CH or Hetar-C(O)C≡CH	Ar or Het	R	Prod.	Yield (%)
1	**1a**	4-NO_2	**19a**		H	**20**	15[b]
2	**1a**	4-NO_2	**19b**		OH	**21**	22[c]
3	**1a**	4-NO_2	**19c**		OH	**22**	32[c,d]
4	**1a**	4-NO_2	**19d**		OH	**23**	41[c]
5	**1b**	4-COOH	**19d**		OH	**24**	64[d,e]
6	**1b**	4-COOH	**19e**		OH	**25**	16[b,e]
7	**1b**	4-COOH	**19f**		H	**26**	37[e,f]
8	**1c**	4-CN	**19f**		H	**27**	39[b]
9	**1d**	4-Br	**19g**		H	**28**	37[c]
10	**1i**	H	**19g**		OH	**29**	38[b]
	1i	H	**19g**		H	**30**	17[b]
11	**1a**	4-NO_2	**19h**		H	**31**	30[b]
12	**1h**	2-NO_2	**19h**		H	**32**	45[b]
13	**1i**	H	**19h**		H	**33**	32[b]
14	**1b**	4-COOH	**19i**		OH	**34**	50[d,e]
15	**1a**	4-NO_2	**19j**		OH	**35**	50[c]
16	**1i**	H	**19j**		H	**36**	53[b]
17	**1j**	2-$COOCH_3$	**19j**		OH	**37**	24[c]
18	**1a**	4-NO_2	**19k**		H	**38**	not isolated[g]

[a]All the reactions, unless otherwise specified, were carried out using ArN=O (1 mmol) and ArC(=O)C≡CH (1 mmol) in 10 - 15 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 recrystallised; [f]product isolated by chromatography.

Some of the indole compounds prepared through this procedure can be furtherly functionalized via reduction steps, alkylative reactions, Michael-type additions, ring closure procedures and rearrangements. *N*-hydroxy-3-aroylindoles

can be extraordinarily versatile tools for many organic transformations and we tested some functional group interconversion reactions only in a preliminary and explorative study. Functionalization procedures were subsequently carried out using *N*-hydroxy-3-aroyl-5-nitroindoles **3 - 5** as starting materials as shown in Scheme 1. The methylation was carried out using potassium carbonate as base and dimethyl sulphate as alkylating agent. The products **39 - 41** were afforded quantitatively, 96% and 89% yields respectively (Scheme 1, (path (a)).

As a model reaction to obtain an aromatic C–H functionalization, substrate **39** was treated with $Mn(OAc)_3$ and dimethyl malonate in acetic acid resulting in a 6-membered ring formation [74], to give the benzo [*b*]-carbazole **42** in 67% yield (Scheme 1, path (b)). This last procedure is an oxidative free radical reaction. Functionalization at C2 on the indole ring was achieved by reaction of **3** with DCC (dicyclohexylcarbodiimide) and triethylamine in acetonitrile as solvent (Scheme 1, path (c)) [75] [76] [77]. The urea-like Compound **43** was efficiently prepared in quantitative yield. Some potentially selective reactions to reduce the N–OH group to N–H were explored: attempts were carried out on compound **3** by using nitrosobenzene, azobenzene and Hantzsch ester (diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate) as reactants with the aim that one of these could play as reductant. However, no reduction of N–OH indoles to N–H indoles was observed. Nevertheless, some recent reports by Wojciechowski, Zhou and Liu and coworkers [78] [79] show that *N*-hydroxyindoles can be selectively and very efficiently reduced using phenacyl bromide and triethylamine at room temperature. Substrate **3** was thus converted to 3-benzoyl-5-nitroindole **44** in 75% yield (Scheme 1, path (d)). *N*-hydroxy-3-benzoyl-5-nitroindole **3** did react as a



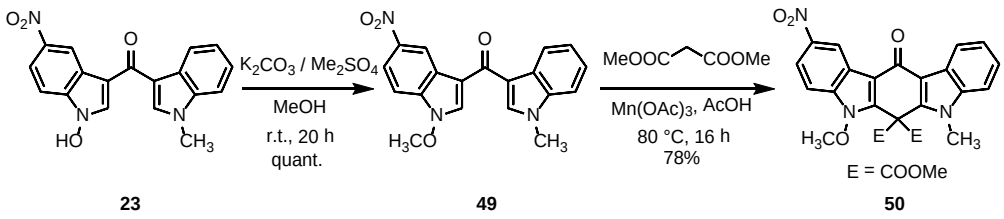
Scheme 1. Functionalization reactions of Compounds **3 - 5**.

nucleophile with Michael acceptors like methyl propiolate **45** and 1-phenyl-prop-2-yn-1-one **2a** by running the reaction in acetonitrile in the presence of DABCO (1,4-diazabicyclo[2.2.2]octane) as base. Products **46** and **47** were respectively obtained in 85% and 80% yield (Scheme 2, path (e)). This kind of reactivity can enable the preparation of a diverse library of compounds by changing both the donor and the acceptor of the Michael-type addition. Another interesting reaction was carried out on Compound **46** by heating it at reflux in CH_3CN and furnishing the indole Compound **48** as the major product in 41% yield through a rearrangement, as reported by Lobo and co-workers (Scheme 1, path(f)) [80].

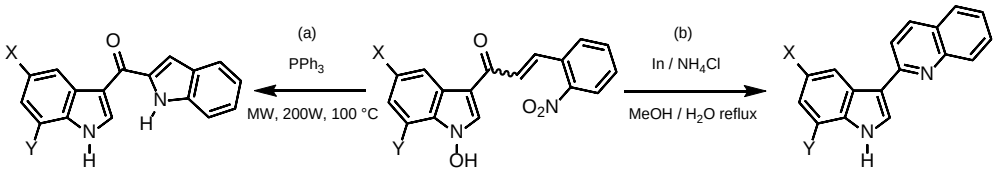
Product **23** (Table 2, entry 4) was tested as a potential precursor to [2,3-*b*]-indolocarbazole. Indolocarbazoles are extremely relevant compounds, since most of them show biological activity and are deeply investigated due to their potential as anti-cancer drugs [81]. Starting from Compound **23**, produced by cycloaddition between **1a** and **19d**, a protective procedure by reaction with K_2CO_3/ Me_2SO_4 was performed affording Compound **49** in quantitative yield. The reaction of **49** with $Mn(OAc)_3$ and dimethyl malonate was finally carried out and led us to isolate the indolo [2,3-*b*]carbazole **50** in 78% yield (Scheme 2).

Moreover, other compounds from Table 2 can be diversely functionalized in different ways. Their versatility led us to explore the opportunity to prepare other annulation products. To our delight, Compound **37** was used to afford biindole product **51** by a Cadogan-Sundberg type cyclization with PPh_3 under microwave irradiation (Scheme 3, path (a)) in 19% yield. Compound **35** was a privileged substrate to get quinoline derivative **52** in 16% yield by reduction with In metal and NH_4Cl in MeOH/H_2O (Scheme 3, path (b)).

We were interested in testing our synthetic protocol using an internal alkynone. A very good opportunity to try this cyclization came from an alternative



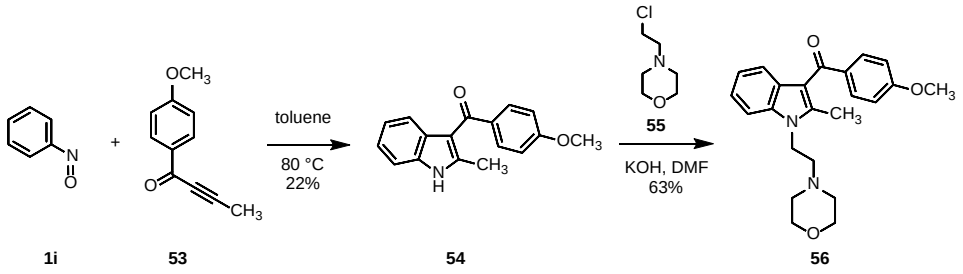
Scheme 2. Synthesis of an Indolo [*2,3-b*]-carbazole.



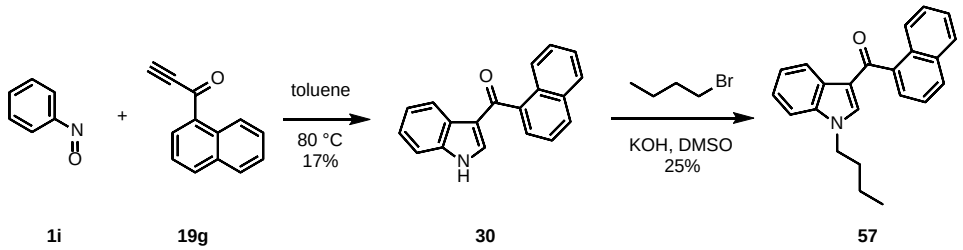
Scheme 3. Syntheses of indole and quinoline derivatives.

synthesis of Pravadoline, an analgesic drug [82] [83] [84] [85], via annulation of nitrosobenzene **1i** with alkynone **53**. Compound **53** was prepared by the addition of prop-1-ynylmagnesium bromide to *p*-anisaldehyde and subsequent oxidation by CrO_3/H_2SO_4 in acetone. Reaction of **53** with nitrosobenzene **1i**, under the standard conditions, furnished indole **54** and this latter compound was subsequently alkylated by reaction with 4-(2-chloroethyl)morpholine **55**, affording pravadoline **56**, but only in 16% overall yield starting from nitrosobenzene (Scheme 4). The synthetic process is unfortunately characterized by an Achilles' heel in the indolization ring closing reaction, the lower reactivity of internal alkynes. Other previous experiments carried out using internal acetylenic derivatives showed lower yields than the reactions with terminal alkynes. Future investigation on the reaction conditions will be devoted to try to improve these results optimizing the products yield.

SAR (Structure-Activity Relationships) studies on novel cannabinoid mimetics revealed that the replacement of the monocyclic 4-methoxybenzoyl group of Pravadoline (Figure 1 and Scheme 4) with a naphthalene moiety increased the potency by nearly 10-fold in the antinociception activity [86]. Among these compounds, 3-naphthoyl indole derivatives were introduced by the Huffman research group, who found a role for this class of molecules as cannabinoid mimetics with interesting selectivity in the interaction with CB1 and CB2 receptors [87]. JWH-018 and JWH-073 are two studied and developed compounds, investigated as synthetic cannabinoids that show a stronger affinity than that of THC for CB1 receptors [88]. With our procedure both JWH-018 [60] and JWH-073 were easily prepared. JWH-073 **57** was synthesized by reaction of nitrosobenzene and 1-naphthoylprop-2-yn-1-one **19g** followed by an alkylative step with *n*-butyl bromide in 25% yield (Scheme 5).



Scheme 4. Alternative synthesis of pravadoline.



Scheme 5. Alternative synthesis of JWH-073.

3. Experimental Section

Representative Procedure for the Synthesis of Indole Compounds

Nitrosoarene (1.0 mmol) and alkynone (1.0 mmol) were combined in toluene (or 1,4-dioxane) (8 ml) under an inert (nitrogen) atmosphere and heated at 80˚C. The reaction was carried out till the complete conversion of the reactants (monitoring by TLC). Products were isolated by filtration or column chromatography. Detailed procedures are reported in **Supplementary Materials**.

4. Conclusion

A substrate survey using different conjugated alkynones and various nitrosoarenes led us to expand the synthetic scope of the indolization procedure obtaining different 3-aroylindole products. The procedure shows a general efficiency and versatility with high functional group tolerance. *N*-hydroxy indoles were afforded as the major products using electron-poor *C*-nitrosoaromatics. Using other nitrosoarenes, N–H indoles were isolated as the major products. The formation of *N*-dehydroxylated products is evidence of a plausible redox step in the reaction mechanism. This step will be further and deeply studied by a mechanistic investigation even using electrochemical methods and voltammetry techniques. So far some initial experiments to determine the presence of oxidized compounds *via* transfer from *N*-hydroxylated products were unfruitful. The annulation occurs through the formation of new N_1–C_2 and new C_3–C_{3a} bonds. A wide library of functionalizable compounds, that could be easily investigated as privileged substrates for the preparation of highly valuable products, was produced. The indole products can be involved in post-cycloaddition procedures affording scaffolds, building blocks, useful reactants, intermediates for ulterior transformations, and fine chemicals that could find application both in materials science and even for medicinal chemistry studies. Due to the biological activity of different 3-acyl- and 3-aroylindoles a direct synthetic route to this class of compounds is a powerful tool for synthetic organic chemistry.

Acknowledgements

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Conflicts of Interest

The authors declare no conflicts of interest.

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Supplementary Materials

In **Supplementary Materials**, characterization of indole compounds and their precursors are provided. Further, images of some synthesized compounds and representative NMR spectra were reported.