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AN EFFICIENT SYNTHESIS OF NEW SPIRO[INDOLO-3(*1H*),2'(*3'H*)-OXADIAZOLYL] AND 1-(TRIAZOL-4-YLMETHYL)ISATIN DERIVATIVES

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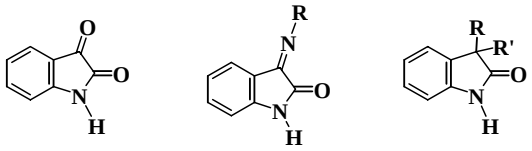
Abstract – The synthesis and the characterization of new isatin derivatives obtained by 1,3-dipolar cycloaddition reactions on allylisatin and propargylisatin are described. The products thus regiospecifically obtained in good yields bear oxadiazolyles or trizolyles groups, and were characterized by FT-IR spectroscopy, NMR spectroscopy and mass spectrometry.

INTRODUCTION

Isatin is well known for its large range of biological activities. Thus, some isatin derivatives (Scheme 1), such as 3-iminoisatin, have found medicinal applications because they possess anticonvulsant,[1] anti-inflammatory[2] and antimicrobial activities,[3] as well as effects on the central nervous system.[4] Moreover, isatin was reported as a product crossing the blood-brain-barrier.[5]

Preliminary biological tests performed in our laboratory have shown that 1-allylisatin has a very low toxicity (0% death for concentrations less than 1 g per kg).[6] *In vivo* tests have demonstrated psychotropic,

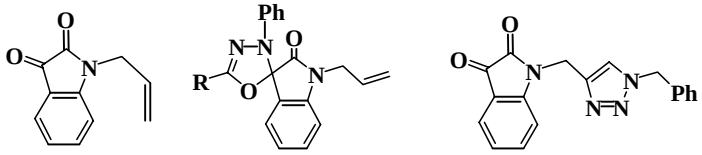
sedative, anxiolytic and anticonvulsivant properties. Moreover, they have shown an increase in hypnotic effects, compared to native isatin activities, and no cataleptic properties.[7]



isatin 3-iminoisatin oxindole

Scheme 1. Isatin and some isatin derivatives.

Based on these results we engaged the synthesis of 1-allylisatin derivatives to obtain new compounds bearing an additional heterocycle able to increase biological activities (Scheme 2). Two sorts of *N*-heterocycles were chosen for their well known biological activities, *i.e.* oxadiazole[8] and triazolylmethyl[9] derivatives.

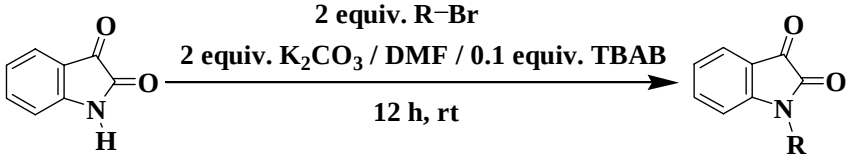


2 5-6 7

Scheme 2. General structure of new isatin derivatives keeping 1-allylisatin skeleton.

RESULTS AND DISCUSSION

The first step was the *N*-alkylation of isatin using corresponding bromides under phase transfer catalysis conditions (Scheme 3).



1 **2-4**

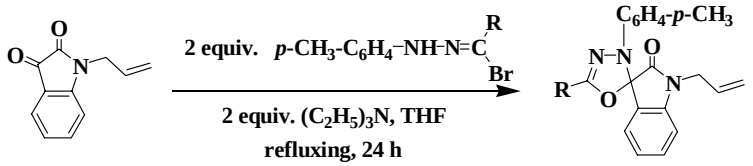
Product	R	Yield (%)
2	CH_2–CH=CH_2	86
3	CH_2–C≡CH	76
4	Bn	90

Scheme 3. *N*-Alkylation of isatin.

In a general procedure, isatin was reacted with allyl bromide, propargyl bromide and benzyl bromide using the mixture K_2CO_3 / DMF / tetrabutylammonium bromide as catalytic system. After 12 h at room temperature and recrystallization from ethanol, 1-allylisatin (**2**) and 1-propargylisatin (**3**) were isolated in

86% and 76% yields respectively. 1-Benzylisatin (**4**) was also synthesized by the same experimental procedure in order to check the importance of the grafting of a heterocycle on biological activity. The product (**4**) was isolated in 90% yield. Each product structure was characterized by traditional spectroscopic methods. FT-IR spectrometry has shown characteristic bands of the grafted moieties (double bound, triple bound or aromatics), and NMR spectrometry confirmed the presence of the allyl, propargyl or benzyl group *N*-grafted on isatin block.

The 1,3-dipolar cycloaddition reactions were first carried out on 1-allylisatin (**2**) (Scheme 4).



2 **5-6**

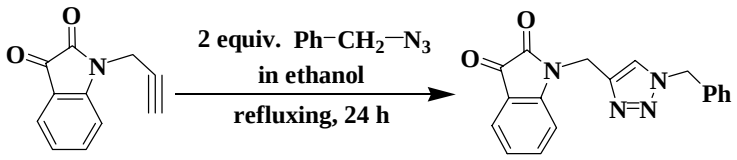
Product	R	Yield (%)
5	Ph	45
6	$CO_2C_2H_5$	58

Scheme 4. Synthesis of oxadiazolyl isatin derivatives from 1-allylisatin (**2**).

The cycloaddition was achieved by refluxing **2** in THF with the *N*-tolyl-*C*-phenylnitrilimine generated *in situ* by the reaction of *N*-tolyl-1-phenylhydrazonyl bromide with triethylamine. The precipitate was purified by recrystallization from ethanol. The desired product 1-allyl-5'-phenyl-3'-(*p*-tolyl)-2*H*-spiro[indolo-3(1*H*),2'(3'*H*)-1,3,4-oxadiazol]-2-one (**5**) was thus obtained in 45% yield.

We performed the same reaction using 2 equiv. of α-bromo-*N*-tolylhydrazonylcarboxylate in the same condition as previously described for the synthesis of **5**. The compound (**6**), ethyl 1-allyl-2-oxo-3'-(*p*-tolyl)spiro[indolo-3(1*H*),2'(3'*H*)-1,3,4-oxadiazole]-5'-carboxylate was isolated in 58% yield. The ethoxycarbonyl substituent of the dipole may have a high mesomeric effect on hydrazone function allowing an easier dipolar attack to 3-carbonyl function of isatin, which could explain the difference in yields between both syntheses. It is important to notice that both reactions leading to the compounds (**5**) and (**6**) have shown a high periselectivity; only the 3-carbonyl group of isatin was attacked, leaving unchanged the carbon-carbon double bond of allylic group. The presence of the double bound was confirmed by FT-IR spectroscopy and NMR spectroscopy, showing the characteristic signals of protons and corresponding carbons of the vinylic function. Moreover, these reactions are regiospecific because the heteroatom of the dipole attacked specifically the 3-carbonyl group of isatin skeleton.

Concerning 1-propargylisatin (**3**), an additional heterocyclic substituent was introduced on its structure by the reaction between the carbon-carbon triple bound and an azide derivative, leading to the isatin derivative (**7**) bearing a triazolyl group (Scheme 5).



3 34% 7

Scheme 5. Synthesis of triazolyl isatin derivative starting from propargylisatin (**3)**.

The azide derivative used in this synthesis was benzyl azide, which was prepared as described by Lindsay *et al*.[10] The desired product 1-(1-benzyl-1,2,3-triazol-4-ylmethyl)indol-2,3-dione (**7**) was obtained in 34% yield. The disappearance of the carbon-carbon triple bond was confirmed by the absence of its FT-IR and ^{1}H and ^{13}C NMR spectra. Again this reaction has shown a high regioselectivity because the compound (**7**) is the only product. This regioselectivity of this 1,3-dipolar cycloaddition reaction was confirmed by ^{13}C NMR spectrum, showing the characteristic signal at 128.2 ppm assigned to C-5 triazolyl carbon, which is in agreement with values found in literature.[11-13] The structure of **7** was also confirmed by NOE experiments showing interactions between hydrogen of CH_2 groups and the hydrogen of the triazolyl cycle.

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EXPERIMENTAL

General

Melting points were determined by differential scanning calorimetry using a Perkin Elmer DSC Pyris 1®. NMR spectra were recorded in $CDCl_3$ (internal Me_4Si) with a Bruker DRX-300 Spectrometer (operating at 300.13 MHz). Elemental analyses were performed by the IUT of Bethune, Departement of Chemistry (Bethune, France). Analytical TLC were performed on Merck aluminium backed silica gel (Silica Gel F254), spots were visualized in UV light. Infra-red spectroscopy was performed using a FT-IR Bruker Vector 22 apparatus equipped with a diamond reflection accessory.

N-Alkylation of isatin

In a general procedure, isatin (1.47 g, 0.01 mol) was reacted with alkyl bromide (0.02 mol) in the presence of K_2CO_3 (2.76 g, 0.02 mol) and tetrabutylammonium bromide (0.32 g, 0.001 mol) in DMF (60 mL). After 12 h stirring at rt, the precipitate was removed by filtration and purified by recrystallization from ethanol.

1-Allylisatin (**2**) was obtained in 86% yield as red crystals, (mp 89-91°C, ethanol). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 4.30 (dd, J = 7.0 and 1.7 Hz, 2H, N-CH_2), 5.24 (m, 2H, CH_2=), 5.78 (m, 1H, -CH=), 6.83-7.51 (m, 4H, H_{Ar}). ^{13}C NMR (300 MHz, $CDCl_3$): δ (ppm) 42.4 (N-CH_2), 110.9, 123.8, 125.2, 138.4 (4 C_{Ar}H), 117.5 (C_{Ar}-C=O), 118.5 (=CH_2), 130.2 (-CH=), 150.8 (C_{Ar}-N-C=O), 157.9 (N-C=O), 183.2 (C=O ketone) ; IR: υ (cm^{-1}) 3093, 1735, 1645, 1601. Anal. Calcd for $C_{11}H_9NO_2$: C; 70.58, H; 4.85, N; 7.48. Found: C; 70.42, H; 4.95, N; 7.60. EIMS $[M]^+$ m/z 187.

1-Propargylisatin (**3**) was obtained in 76% yield as orange crystals (mp 156-158°C, ethanol). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 4.50 (d, J = 2.6 Hz, 2H, N-CH_2), 2.32 (t, J=2.6 Hz, 1H, ≡CH), 7.20-7.63 (m, 4H, H_{Ar}). ^{13}C NMR (300 MHz, $CDCl_3$): δ (ppm) 29.8 (N-CH_2), 73.9 (≡CH), 74.5 (-C≡), 111.7, 125.8, 126.2, 139.3 (4 C_{Ar}-H), 117.4 (C_{Ar}-C=O), 149.0 (C_{Ar}-N-C=O), 158.6 (N-C=O), 183.0 (C=O ketone) ; IR: υ (cm^{-1}) 3243, 2117, 1728, 1601. Anal. Calcd for $C_{11}H_7NO_2$: C; 71.35, H; 3.81, N; 7.56. Found: C; 71.50, H; 3.72, N; 7.75. EIMS $[M]^+$ m/z 185.

***N*-Benzylisatin** (**4**) was obtained in 80% yield as orange crystals (mp 133-135°C, ethanol). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 4.86 (s, 2H, N-CH_2), 6.70-7.55 (m, 9H, H_{ar}) ; ^{13}C NMR (300 MHz, $CDCl_3$): δ (ppm) 44.0 (N-CH_2), 111.0, 123.9, 125.4, 138.3 (4 C_{Ar}), 127.4, 128.2, 129.1 (3 C_{Bn}), 117.7, (C_{Ar}-C=O), 134.5 (C_{qBn}), 150.7 (C_{Ar}-N-C=O), 158.3 (N-C=O), 183.3 (C=O ketone) ; IR: υ (cm^{-1}) 3030, 1727, 1608. Anal. Calcd for $C_{15}H_{11}NO_2$: C; 75.94, H; 4.67, N, 5.90. Found: C; 76.08, H; 4.52, N; 6.05. EIMS $[M]^+$ m/z 237.

1,3-Dipolar cycloaddition reactions starting from compound (2)

1-Allyl-5'-phenyl-3'-(*p*-tolyl)-2*H*-spiro[indolo-3(1*H*),2'(3'*H*)-1,3,4-oxadiazol]-2-one (**5**) was obtained by refluxing compound (**2**) (1.87 g, 0.01 mol) for 24 h with *N*-tolyl-1-phenylhydrazonyl bromide (5.48 g, 0.02 mol) and triethylamine (2.02 g, 0.02 mol) in THF (60 mL). The precipitate was recovered by filtration and was purified by recrystallization from ethanol. Product (**5**) was thus obtained in 45% yield as yellow crystals (mp 176-178°C, ethanol). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.36 (s, 3H, C_{Ar}-CH_3), 3.87 (dd, J = 6.9 and 1.8 Hz, 2H, N-CH_2), 5.26 (m, 2H, =CH_2), 6.02 (m, 1H, =CH), 6.35-7.50 (m, 13H, H_{Ar}). ^{13}C NMR (300 MHz, $CDCl_3$): δ (ppm) 14.3 (CH_3), 46.2 (N-CH_2), 109.8, 116.3, 135.7, 139.7, 145.1, 147.6, 153.6 (Cq), 112.0, 125.5, 126.8, 127.9, 130.2, 130.6, 132.0, 135.1, 137.4 (C_{Ar}H), 115.7 (=CH_2), 129.0 (=CH-), 154.7 (C=O amide) ; IR: υ (cm^{-1}) 3085, 3029, 2975-2831, 1643, 1612. Anal. Calcd for Elemental Analysis $C_{25}H_{21}N_3O_2$: C; 75.93, H; 5.35, N: 10.63. Found: C; 75.72, H; 5.43, N; 10.70. EIMS $[M]^+$ m/z 395.

Ethyl 1-allyl-2-oxo-3'-(*p*-tolyl)spiro[indolo-3(1*H*),2'(3'*H*)-1,3,4-oxadiazole]-5'-carboxylate (**6**) was obtained using the same procedure as previously, by reaction of (**2**) (1.87 g, 0.01 mol) with α-bromo-*N*-tolyl-hydrazonylcarboxylate (5.40 g, 0.02 mol). Product (**6**) was purified by recrystallization

from ethanol and obtained in 58% yield as yellow crystals (mp 187-189°C, ethanol). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.42 (t, J = 7.1 Hz, 3H, O-C-CH_3), 2.38 (s, 3H, C_{Ar}-CH_3), 3.85 (dd, J = 7.1 and 1.7 Hz, N-CH_2), 4.56 (q, J = 7.1 Hz, 2H, O-CH_2), 5.28 (m, 2H, =CH_2), 6.05 (m, 1H, =CH), 6.45-7.40 (m, 8H, H_{Ar}). ^{13}C NMR (300 MHz, $CDCl_3$): δ (ppm) 14.7 (CH_3), 21.6 (CH_3-C-O), 46.1 (N-CH_2), 62.4 (O-CH_2), 109.9, 116.3, 135.9, 139.8, 147.6, 153.8 (C_q), 112.1, 125.6, 130.3, 130.7, 132.1, 135.1 (C_{Ar}H), 115.7 (=CH_2), 129.1 (=CH-), 160.3 (C=O ester), 154.6 (C=O amide) ; IR: υ (cm-1) 3080, 2982-2820, 1726, 1644, 1609. Anal. Calcd for $C_{22}H_{21}N_3O_4$: C; 67.51, H; 5.41, N; 10.74, Found: C; 67.62, H; 5.28, N; 10.85. EIMS $[M]^+$ m/z 391.

1,3-Dipolar cycloaddition reactions starting from compound (3)

1-(-1-Benzyl-1,2,3-triazol-4-ylmethyl)indol-2,3-dione (**7**) was obtained by refluxing (**3**) (1.85 g, 0.01 mol) with benzyl azide (2.66 g, 0.02 mol) in ethanol (30 mL) for 24 h. After cooling the reaction medium to rt, the precipitate was washed with ethanol. The desired product (**7**) was obtained with 34% yield as a yellow crystals (mp 139-141°C, ethanol). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 4.95 (s, 2H, OC-N-CH_2), 5.46 (s, 2H, N-CH_2-Ph), 7.20-7.60 (m, 9H, H_{Ar}), 7.54 (s, 1H, $CH_{triazole}$). ^{13}C NMR (300 MHz, $CDCl_3$): δ (ppm) 35.8 (OC-N-CH_2), 54.8 (N-CH_2-Ph), 111.9, 124.4, 125.6, 139.0 (C_{Ar}H isatin), 117.9 (C_{Ar}-CO), 128.2 ($C_{triazole}$H), 128.6, 139.3, 129.6 (C_{Ar}H benzyl), 134.4 (Cq benzyl), 150.6 (C_{Ar}-N), 158.3 (C=O amide), 183.5 (C=O ketone) ; IR: υ (cm^{-1}) 3126, 1737, 1609. Anal. Calcd for $C_{18}H_{14}N_4O_2$: C; 67.91; H; 4.43, N; 17.60%. Found: C; 68.07, H; 4.27, N; 17.45. EIMS $[M]^+$ m/z 318.

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