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Graphical Abstract

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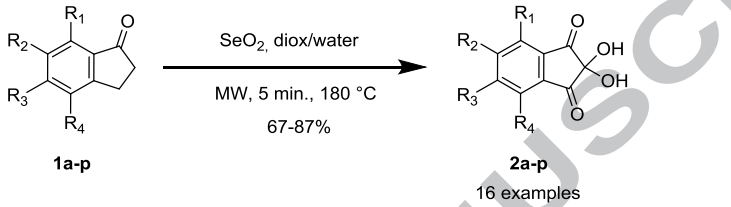

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Microwave-Assisted Oxidation of Indan-1-ones into Ninhydrins

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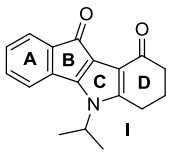
ABSTRACT

A simple and general microwave-assisted selenium oxidation has been developed for the synthesis of substituted ninhydrins from indan-1-ones in order to access to indeno[1,2-*b*]indoles substituted on the A ring. This efficient and convenient oxidation, using selenium dioxide under microwave irradiations, afforded mono- and di-substituted ninhydrins in a single step reaction with good yields.

Protein kinase CK2 (formally termed casein kinase 2) is an essential, ubiquitous serine/threonine kinase which is highly pleiotropic, and constitutively active.[1] A high activity of this protein has been reported in many human diseases[2] such as inflammatory disease processes, neurodegenerative disorders, viral infections and cardiovascular diseases. Moreover, CK2 has been associated with the proliferative status of several tumor cells from breast, colon, kidney, lung, pancreas and prostate.[3] In most cases a remarkable hyperactivity of CK2 has been observed.



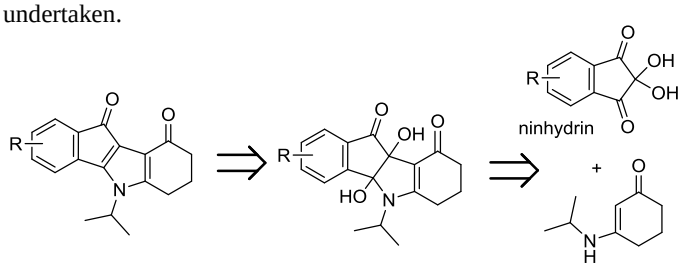
I

Figure 1 5-Isopropyl-5,6,7,8-tetrahydroindeno[1,2-*b*]indole-9,10-(5*H*,6*H*)dione (**I**)

To date, numerous compounds have been identified as CK2 inhibitors.[4] Among them, the indeno[1,2-*b*]indole derivatives have revealed a great interest as ATP-competitive inhibitors,[5] effectively reducing cell viability and causing cell death. These compounds consist of small and planar heterocyclic scaffolds, which are able to fit into the nucleotide-binding pocket of CK2α and displace the ATP. The most potent CK2 inhibitor (**I**) (Figure 1) in this series inhibits the human CK2 with an IC_{50} of 0.11 µM and presents very good kinase selectivity.[6]

Its preparation was achieved in two steps from commercial ninhydrin, following the general pathway (R=H) which is described in the retrosynthetic scheme 1.[7]

In order to draw up Structure-Activity Relationships (SAR) to evaluate the influence of the nature and the position of substituants on the A ring, the synthesis of new substituted ninhydrins derivatives (R= OH, OMe, NO_2, Br, F, CF_3) was undertaken.



Scheme 1 Retrosynthetic Analysis of Indeno[1,2-*b*]indole Derivatives

Ninhydrin (2,2-dihydroxyindane-1,3-dione) is well-known in particular owing to its color-forming reaction with amines.[8] Due to this property, numerous ninhydrins analogues have been reported for their use as latent fingerprint detectors in forensic science.[9] Ninhydrins are also used for the synthesis of heterocyclic compounds.[10] They are usually prepared by oxidation of indan-1-ones or indane-1,3-diones (Scheme 2).

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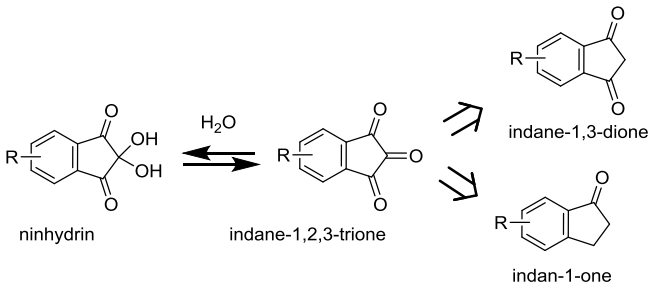
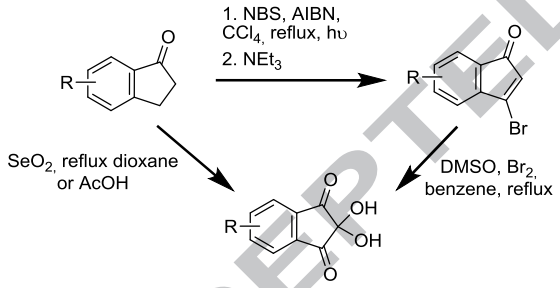


Scheme 2 Retrosynthetic Analysis of Ninhydrins

Indan-1-ones are widely described as synthetic intermediates.[11] In addition, many of them are commercially available which prompted us to use them as starting material. Different methods are reported in the literature to oxidize indan-1-ones into 1,2,3-triones[12] which lead, in the presence of water, to an equilibrium with their more stable monohydrated form, the ninhydrin (Scheme 2).[13]

A first approach applies a sequence bromination / Kornblum-type oxidation of indan-1-ones (Scheme 3).[9b, 10c, 14]
An alternative way allows direct oxidation of indan-1-ones into ninhydrins by selenium dioxide, which is the most common reagent used for oxidation of alkyl fragments, in particular to convert mono carbonyl derivatives into 1,2-dicarbonyl compounds.[15] 5-*O*-alkylated ninhydrins were prepared with good yields (54-81%) using from 3 to 5 equivalents of selenium dioxide in dioxane at reflux for 3 to 6 hours.[16]

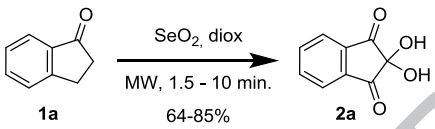


Scheme 3 Ninhydrins Syntheses from Indan-1-ones

Microwave-assisted organic synthesis (MAOS) takes on great interest, which is evidenced by the large number of papers and reviews describing decreased reaction time, limited waste, increased yield and limited degradation.[17] This non-classical heating technique has been adopted in many academic and industrial laboratories. Moreover, selenium dioxide oxidation by closed-vessel microwave is reported to accelerate the synthesis of 1,2-dicarbonyl compounds.[18] A first attempt to oxidize 5-bromoindan-1-one using 3.1 equivalents of selenium dioxide in a sealed vessel under microwave heating in a Biotage Initiator Microwave synthesizer 2.0 440 W, at 170 °C in dioxane for ninety seconds afforded the 5-bromoninhydrin **2j** with 60% yield. This yield was significantly higher than the 23% yield obtained by Joullié *et al.* using 6-bromoindan-1-one and 5 equivalents of selenium dioxide, in dioxane at reflux for 2h.[9b] No workup was required: purification was simplified by a better conversion of selenium to selenium black. The product was only purified by column chromatography using solid deposit.

This result led us to explore the oxidation of indan-1-one **1a** to ninhydrin **2a** under microwave heating by varying the time and the number of equivalents of selenium dioxide (Table 1).

Table 1 Optimization of Reaction Conditions



Entry	SeO_2 (equiv.)	Water	Temp. (°C)	Time (min)	Yield %
1	3.1	-	classic, 100	45	64
2	3.1	-	classic, 100	210	71
3	3.1	-	MW, 180	1.5	72
4	3.1	-	MW, 180	5	78
5	3.1	-	MW, 180	10	81
6	2.5	-	MW, 180	5	67
7	4.6	-	MW, 180	5	79
8	3.1	10%	MW, 180	5	84
9	3.1	10%	MW, 180	10	85
10	3.1	10%	sealed-vessel, 180	5	33
11	3.1	10%	sealed-vessel, 180	20	77

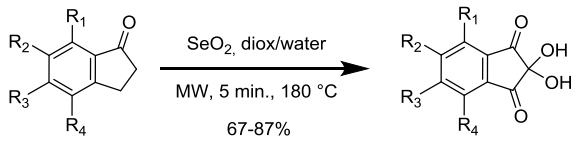
Conventional and microwave heating (Table 1, entries 1-3) were first compared. The same yield was obtained even though microwave process remarkably reduced the reaction time (210 minutes to 1.5 minute). The increase in microwave irradiation time (Table 1, entries 3-5) improved the yields (from 72 to 81%). Variation of the number of equivalents of selenium dioxide (Table 1, entries 4, 6 and 7) pointed out that 3.1 equivalents were necessary but sufficient. The addition of water (10%) also improved the yield (Table 1, compare entries 4 to 8 and 5 to 9), which was probably due to the more elevated pressure in the vessel (8 bar to 13-16 bar). These conditions allowed us to get roughly the same yield, as the reaction time lasted five or ten minutes (Table 1, compare entries 8 and 9), which suggests that five minutes are sufficient.
In order to evaluate the influence of the thermal character, we applied the best conditions 8, using a sealed-vessel heated conventionally at 180°C for 5 and 20 minutes respectively (Table 1, entries 10 and 11). The yields were systematically lower, (77 % versus 84 %) suggesting a role of microwaves in this oxidation.

Then, to assess the scope of this method, we applied entry 8 to several substituted indan-1-ones. All ninhydrins (Table 2) were obtained with good to excellent yields (66-87%), always enhanced compared to those reported in the literature, after a purification step.[19] This closed-vessel microwave selenium dioxide oxidation has proved to be a general and convenient method.

In conclusion, we improved the classical oxidation conditions of indan-1-ones into ninhydrins by using microwave irradiations. We developed a rapid, convenient and general oxidation method, limiting amounts of selenium dioxide. These conditions, applied to substituted indan-1-ones, will be used to rapidly and easily

prepare diverse substituted ninhydrins in a single step with very good yields.

Table 2 Oxidation of Several Indan-1-ones



1a-p **2a-p**

Ninhydrin 2	R_1	R_2	R_3	R_4	Yield (%)	Yield (%) lit.	N° ref. lit.
2a	H	H	H	H	84	85[a]	13
2b	H	H	H	Me	79	21[a]	10c
2c	H	H	H	Br	70	#[c]	9d, 9e
2d	F	H	H	H	81	#[c]	10d, 10e
2e	H	H	H	CF_3	66		nd
2f	H	H	H	NO_2	74	100[a*]	10a
2g	H	H	H	OH	74	#[c]	10b
2h	H	H	H	OMe	87	58[b]	9d
2i	H	Me	H	H	87	61[a]	10c
2j	H	H	Br	H	80	45[a]	10c
2k	H	F	H	H	86	40[a]	10c
2l	H	NO_2	H	H	70	#[c]	9d, 9e
2m	H	H	OH	H	73	27[b]	10f
2n	H	H	OMe	H	85	73[a]	16a
2o	OMe	H	H	OMe	67		nd
2p	H	OMe	OMe	H	80	53[a]	14c

[a]: yield described from the corresponding indanone; the oxidation method could be different; [b]: yield not described from the corresponding indanone; yield described from the corresponding indane-1,3-dione; [c]: yied not specified; [*]: described without any purification; nd : not described

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.

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18. *General experimental procedure for the synthesis of the ninhydrins (**2**)*: A sealed-pressurised reaction vessel (5 mL) equipped with a magnetic stirrer was charged with indan-1-one (1 eq.), selenium dioxide (3.1 eq.) and dioxane/water (3 mL/0.3 mL). It was then irradiated in a Biotage Initiator Microwave synthesizer 2.0 440 W with microwave heating to 180 °C with a maximum of 400 W for 5 minutes. Then, the vessel was rapidly forced-air cooled to room temperature. The mixture was transferred into a round bottom flask, and the vessel washed with acetone. Silica was added to prepare a solid deposit. The volatile solvents were then evaporated *in vacuo* before purification by flash chromatography (ethyl acetate / cyclohexane) to afford the corresponding ninhydrin.