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Reduction of 3-nitrophthalic anhydride by $SnCl_2$ in different alcohols: a simple synthesis of alkyl 1,3-dihydro-3-oxo-2,1-benzisoxazole-4-carboxylates

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ABSTRACT

A new, mild and efficient process is developed for the synthesis of alkyl 1,3-dihydro-3-oxo-2,1-benzisoxazole-4-carboxylates through the reduction of 3-nitrophthalic anhydride by $SnCl_2$ in different alcohols. The synthesis of benzisoxazoles bearing a sulfonamide functionality is also reported. The structure of sulfonamide **8d** is confirmed by X-ray diffraction analysis.

Reduction of aromatic nitro compounds to the corresponding amines is an important transformation in synthetic organic chemistry. Numerous methods for the direct reduction of aromatic nitro compounds to amines have been well documented.[1–3]

We reported previously the reduction of some nitroindazoles with anhydrous $SnCl_2$ in various alcohols, in the presence of arylsulfonyl chlorides and pyridine.[4] Thus, we observed a new kind of transformation: 4-, 6- and 7-nitroindazoles, by the action of $SnCl_2$/EtOH, gave 4- or 7-ethoxy aminoindazoles, probably via an oxidative nucleophilic substitution of hydrogen (ONSH),[5] together with the expected 4-, 6- and 7-aminoindazoles (Scheme 1).

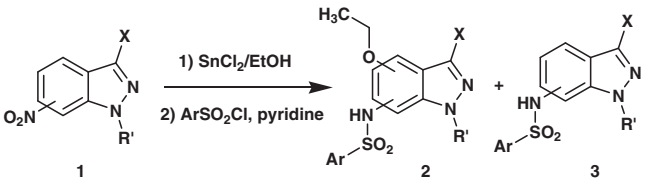
As significant degradation of the obtained aromatic primary amines was observed, we decided to protect them by treatment with an arylsulfonyl chloride in the presence of pyridine. Arylsulfonyl chlorides were chosen in our previous studies, and we found that *N*-[7(6)-indazolyl]arylsulfonamides[6] showed important antiproliferative activity against some human and murine cell lines.

As an extension of these results, in the present work, we investigated the reduction of other aromatic nitro compounds under similar experimental conditions. Thus, we report our detailed studies on the reduction of 3-nitrophthalic anhydride by $SnCl_2$ in different alcohols.

The reduction of 3-nitrophthalic anhydride (**4**) afforded, in all cases, a mixture of two compounds: the expected amine **5**[7] and, interestingly, as a function of the present alcohols, the unexpected compounds **6a–d**. On the basis of ^1H, ^{13}C NMR and MS data, we propose compounds **6a–d** as alkyl 1,3-dihydro-3-oxo-2,1-benzisoxazole-4-carboxylates (Scheme 2). No trace of the alkoxy aminophthalic anhydride **7** was found.

In the literature, the only successful cyclisation giving 2,1-benzisoxazolinone was the reduction of 3-nitrophthalic acid reported by Woolley in a 1958 patent.[8]

As shown in Table 1, the reduction of compound **4** with $SnCl_2$ in different alcohols led to different yields of products **5** and **6** after separation by flash chromatography. We observed that, the reduc-



Scheme 1. Reduction of nitroindazoles with $SnCl_2$ in ethanol.

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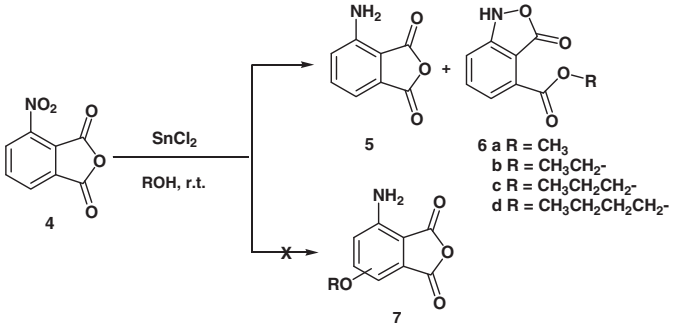
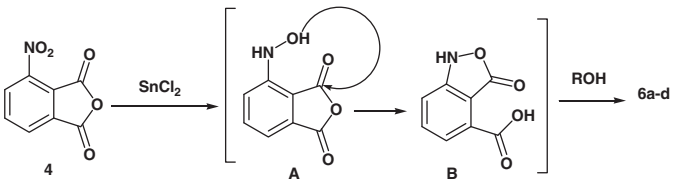


Scheme 2. Reduction of 3-nitrophthalic anhydride with $SnCl_2$ in different alcohols.

Table 1
Reduction of **4** with $SnCl_2$ in different alcohols

R	Yield of **5**[a] (%)	Mp (°C)	Yield of **6**[a] (%)	Mp (°C)
CH_3	42	250–252	44 (**6a**)	103–105
CH_3CH_2	28	—	35 (**6b**)	88–90
$CH_3(CH_2)_2$	31	—	36 (**6c**)	42–44
$CH_3(CH_2)_3$	26	—	37 (**6d**)	44–46

[a] Isolated yield after separation by flash chromatography.



Scheme 3. A plausible mechanism for the reduction of 3-nitrophthalic anhydride with $SnCl_2$ in different alcohols.

tive heterocyclisation reaction of **4** in the presence of methanol as the solvent gave the benzisoxazole with the best yield (44%). Presumably, this could be related to the ability of methanol to dissolve $SnCl_2$. Stoichiometrically, this reaction requires just 2 equiv of $SnCl_2$ for the reduction of the nitro group, but in practice, a large excess gave better yields and reduced the reaction times.

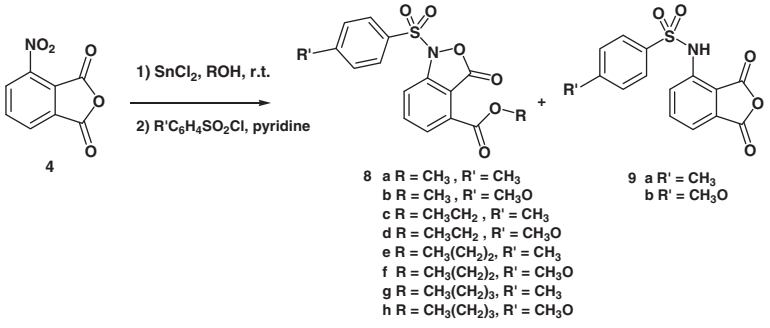
The formation of alkyl 1,3-dihydro-3-oxo-2,1-benzisoxazole-4-carboxylates **6a–d** can be explained by the mechanism shown in Scheme 3. The reduction of 3-nitrophthalic anhydride with tin(II) chloride in a protic solvent such as an alcohol presumably proceeds by way of the hydroxylamine-like intermediate **A**, which in turn undergoes an intramolecular cyclisation (an S_NAc process), followed by esterification of the intermediate acid **B** to give the products **6a–d**.

1,2-Benzisoxazoles and their derivatives show interesting pharmacological and biological activities.[9] One such example bearing a sulfonamide functionality is Zonisamide (benzo[*d*]isoxazol-3-ylmethanesulfonamide) which is used as an antiepileptic drug.[10]

Along these lines, and searching for the synthesis of new 1-arylsulfonyl-1,3-dihydro-3-oxo-2,1-benzisoxazoles, which are useful for biological screening, we examined the reduction of 3-nitrophthalic anhydride (**4**) with $SnCl_2$ in different alcohols, followed by coupling of the obtained amines with various arylsulfonyl chlorides in pyridine.[11,12] However, in all cases, we isolated a mixture of the two sulfonamides **8** and **9** in good to excellent combined yields (57–84%; Scheme 4 and Table 2). We are now investigating the experimental conditions in order to address the course of the reaction, essentially towards the formation of the most interesting compounds **8a–h**.

The structures of products **8** and **9** were determined from their ^1H NMR and ^{13}C NMR spectra and by MS. The structure of **8d** was further confirmed by X-ray diffraction analysis[13] (Fig. 1).

In summary, we have described an efficient synthesis of some new alkyl 1-arylsulfonyl-1,3-dihydro-3-oxo-2,1-benzisoxazole-4-carboxylates and 4-arylsulfonamido-1,3-isobenzofurandiones by



Scheme 4. Reduction of **4** in different alcohols and protection with arylsulfonyl chlorides in pyridine.

Table 2
Reduction of **4** in different alcohols and protection with arylsulfonyl chlorides in pyridine

Entry	R	R′	Yield of **8**[a] (%)	Mp (°C)	Yield of **9**[a] (%)	Mp (°C)
1	CH_3	CH_3	42 (**8a**)	75–77	38 (**9a**)	96–98
2	CH_3	CH_3O	46 (**8b**)	129–131	35 (**9b**)	114–116
3	CH_3CH_2	CH_3	40 (**8c**)	93–95	32 (**9a**)	96–98
4	CH_3CH_2	CH_3O	48 (**8d**)	122–124	36 (**9b**)	114–116
5	$CH_3(CH_2)_2$	CH_3	36 (**8e**)	44–46	26 (**9a**)	96–98
6	$CH_3(CH_2)_2$	CH_3O	50 (**8f**)	58–60	31 (**9b**)	114–116
7	$CH_3(CH_2)_3$	CH_3	38 (**8g**)	59–61	19 (**9a**)	96–98
8	$CH_3(CH_2)_3$	CH_3O	46 (**8h**)	80–82	30 (**9b**)	114–116

[a] Isolated yields over the two steps after separation by flash chromatography.

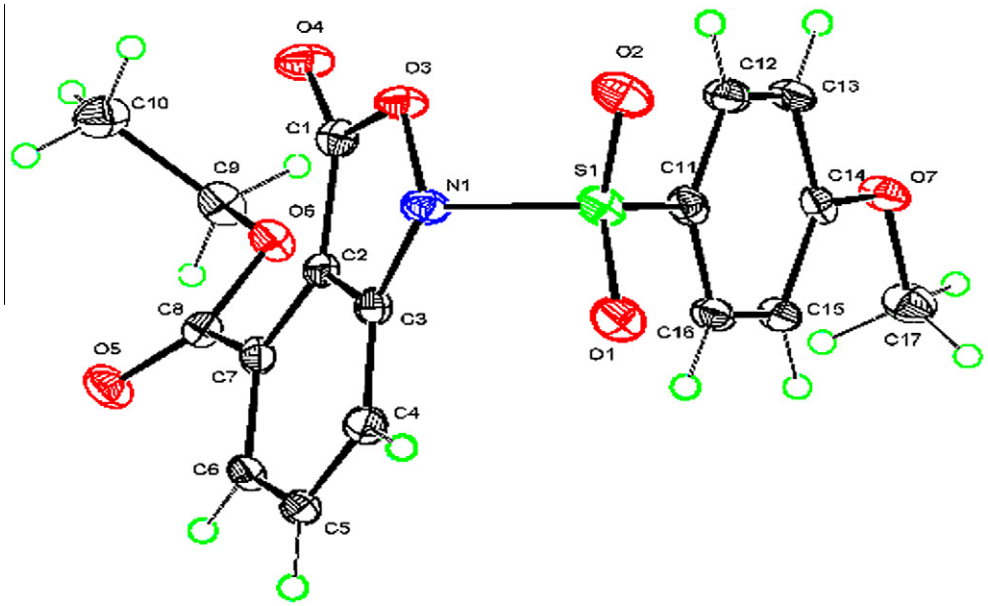


Figure 1. X-ray crystal structure of compound **8d**.

simple reduction of 3-nitrophthalic anhydride in different alcohols, and protection with an arylsulfonyl chloride. This appears to be a general method to prepare new building blocks of possible interest in medicinal chemistry.

Of particular interest appears the formation of compounds **8**. As a matter of fact, their benzene ring is substituted with an arylsulfonamide functionality which represents a very 'important' pharmacophore,[14] and by an ester functionality that can be modified by a series of S_NAc (nucleophilic acyl substitution) reactions, or via different reduction or coupling processes. Moreover, compounds **9** present interesting modes of reactivity strictly related to the presence of a heterocyclic ring.

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Supplementary data

Supplementary data (relevant spectra, ^1H, ^{13}C NMR and DEPT for selected compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.01.037.

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11. *General procedure for the synthesis of compounds **5** and **6a–d**, **8a–h** and **9a,b**.* A mixture of 3-nitrophthalic anhydride (0.5 g, 2.6 mmol) and $SnCl_2$ (2.9 g, 15.5 mmol) in 20 mL of alcohol was stirred at room temperature. After the reduction, the pH was made slightly basic (pH 7.2–8.0) by the addition of 5% aqueous $KHCO_3$ before extraction with EtOAc (3 × 50 mL). The organic phase was dried over $MgSO_4$. At this point the synthesis of **5** and **6a–d** was achieved and they could be obtained from the crude by flash chromatography by elution with a mixture of EtOAc/hexane (1:9). The solvent was removed to afford the amine, which was immediately dissolved in pyridine (10 mL) and then treated with the arylsulfonyl chloride (1.1 equiv). The reaction mixture was stirred at room temperature overnight, and then concentrated in vacuo. The resulting residue was purified by flash chromatography by elution with a mixture of EtOAc/hexane (1:9).
12. (a) *Characterisation data for compound **8d***: ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.36 (t, 3H, J = 7.2 Hz, CH_3), 3.82 (s, 3H, CH_3O), 4.37 (q, 2H, J = 7.2 Hz, CH_2O), 6.84 (d, 2H, J = 9 Hz, HAr), 7.60 (d, 2H, J = 9 Hz, HAr), 7.78–7.84 (m, 2H, HAr), 8.05 (dd, 1H, J = 6.8 Hz, HAr); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 13.9 (CH_3), 55.8 (CH_3O), 62.3 (CH_2O), 112.4 (Cq), 114.6 (2CH), 119.8 (CH), 121.7 (Cq), 128.9 (CH), 131.5 (Cq), 131.8 (2CH), 135.4 (CH), 150.7 (Cq), 162.7 (Cq), 163.9 (CO), 165.2 (CO); EI-MS (m/z): 378 $(M+H)^+$. Anal. Calcd for $C_{17}H_{15}NO_7S$: C, 54.11; H, 4.01; N, 3.71. Found: C, 54.25; H, 3.83; N, 3.65. (b) *Characterisation data for compound **9b***: ^1H NMR (DMSO-d_6, 300 MHz) δ: 3.78 (s, 3H, CH_3O), 7.05 (d, 2H, J = 9 Hz, HAr), 7.56 (d, 2H, J = 9 Hz, HAr), 7.71–7.75 (m, 1H, HAr), 7.96–8.01 (m, 2H, HAr), 8.58 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ: 56.5 (CH_3O), 111.0 (Cq), 115.6 (2CH), 119.1 (CH), 120.7 (Cq), 128.7 (CH), 131.2 (Cq), 132.2 (2CH), 137.5 (CH), 150.1 (Cq), 163.1 (Cq), 165.6 (CO), 165.7 (CO); EI-MS (m/z): 334 $(M+H)^+$. Anal. Calcd for $C_{15}H_{11}NO_6S$: C, 54.05; H, 3.33; N, 4.20. Found: C, 54.18; H, 3.42; N, 4.08.
13. *Crystal structure data for compound **8d***: Crystals of $C_{17}H_{15}NO_7S$ belong to the $P\bar{1}$ space group [a = 8.2245 (4), b = 10.4699 (5), c = 10.4795 (5) Å, α = 78.547 (2), β = 69.084 (2), γ = 80.925 (2)°; Z = 2; V = 822.41 (7) Å^3]. The 7636 room-temperature diffraction data were measured on a Bruker X8 diffractometer using Mo Kα radiation up to a 2-θ max of 52.04°. The crystal structure was refined to a final R-index of 0.0404 for 3041 unique reflections and 237 least-squares parameters. The crystallographic information file has been deposited with the Cambridge Crystallographic Data Centre, CCDC 903962.
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