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A facile synthesis of 4- and 6-chloromethyl-1*H*-indole-2-carboxylates: replacement of a sulfonic acid functionality by chlorine

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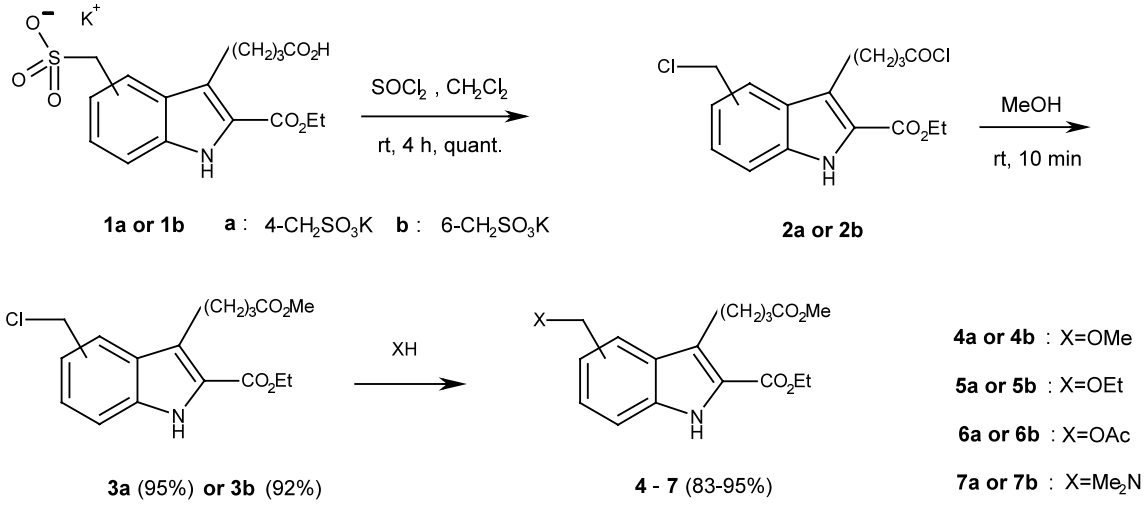
Abstract—Valuable new synthetic intermediates, 4- or 6-chloromethyl-1*H*-indole-2-carboxylates, were prepared by the elimination of SO_2 from 2-ethoxycarbonyl-1*H*-indole-4- or 6-methanesulfonic acids, respectively, which are easily accessible by Fischer-type indolization.

The synthesis of highly substituted indoles has been a goal of organic chemists for many years.[1] The direct introduction of substituents onto the benzene part of an already constructed indole always raises the question of appropriate regioselectivity. This is well known from works dealing with the Friedel–Crafts-type acylation of indoles.[2] In most cases it seems more useful to introduce the desired functionalities prior to the elaboration of the indole ring. Due to the rather harsh conditions required during the indolization step it is necessary to utilize fairly robust benzenoid precursors compatible with the required conditions. Elaboration to the more reactive functionalities actually found in the targeted indoles is then often a multistep procedure and inefficient in yield.

In this paper we demonstrate that the sulfomethyl group while being extremely stable as a benzenoid or



Scheme 1.

Keywords: Fischer synthesis; 4-(chloromethyl)indoles; 6-(chloromethyl)indoles; desulfination.

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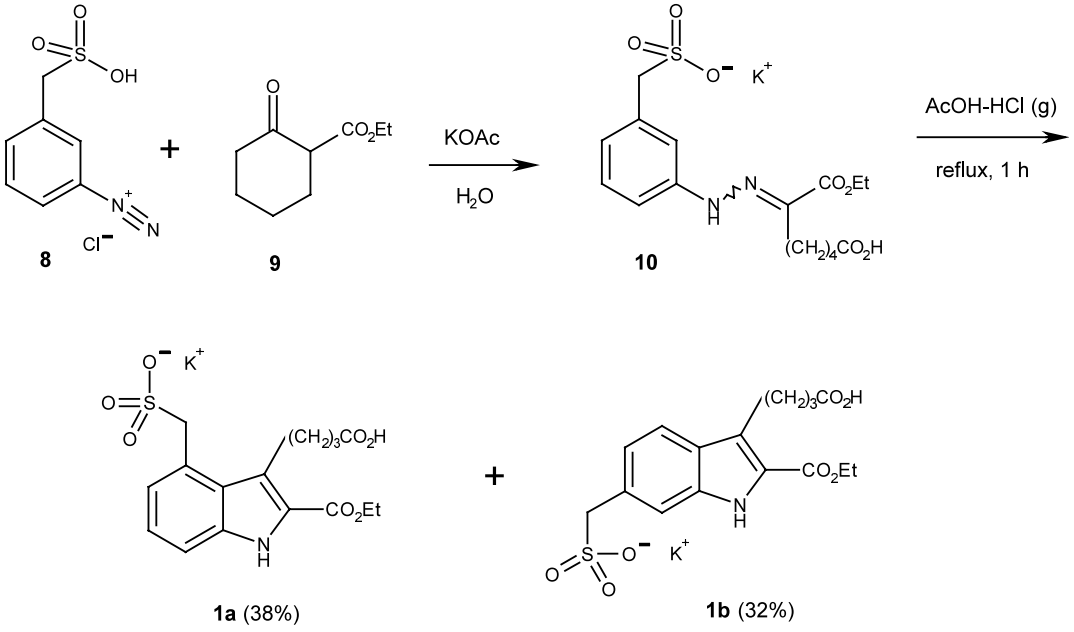
indole substituent, can easily be transformed into a 4- or 6-chloromethyl group in 2-ethoxycarbonyl-1*H*-indole-4- or 6-methanesulfonic acids, respectively. Earlier we reported[3] that the 2-ethoxycarbonyl-1*H*-indole-5-methanesulfonic acids were easily transformed into 5-chloromethyl-1*H*-indole-2-carboxylates using typical conditions for the formation of sulfonyl chlorides. It was suggested[3] that a 'gramine type' resonance interaction must facilitate the elimination of SO_2 from the 5-indolylcarbinyl carbon in 2-ethoxycarbonyl-1*H*-indole-5-methanesulfonic acids. This was by analogy with the facile loss of SO_2 from 2-(phenylthio)ethanesulfonates[4] or aryloxymethanesulfonates[5] explained by the intermediacy of episulfonium-, or $[ArO^+{=}CH_2]$ ions, respectively. According to this explanation the preferred compounds that undergo this type of elimination would be indole-5- and indole-7-methanesulfonic acids. To prove this mechanism we have synthesized indole-4- and indole-6-methanesulfonic acids **1a**,**b** with the expectation that they will behave like normal sulfonic acids yielding sulfonyl chlorides with $SOCl_2$.

Suprisingly, we found that **1a**,**b** underwent the same type of elimination under the influence of $SOCl_2$ more readily than the indole-5-methanesulfonic acids, with concomitant formation of 4- and 6-(chloromethyl)-indoles (Scheme 1).

The elimination and replacement of the SO_3 group by chlorine in **1a**,**b** is actually so facile that the SO_3 group may be regarded as a kind of latent chlorine atom. During chlorination (Scheme 1), the 3-carboxypropyl groups of **1a**,**b** are transformed to acid chlorides **2a**,**b** and undergo methanolysis much faster than the chloromethyl group. The chloromethyl indoles **3a**,**b** are reactive compounds that easily react with alcohols at rt even in the absence of base to give **4** and **5**; and with NaOAc/AcOH or Me_2NH/H_2O[6,7] to give **6** and **7**, respectively (Scheme 1). Compared to ethyl 3-[3-(chlorocarbonyl)propyl]-5-(chloromethyl)-1*H*-indole-2-carboxylate, however, they appear to be less reactive. With this compound, the stepwise methanolysis of COCl and 5-CH_2Cl, according to the process **2** to **3**, then **4** cannot be carried out as the two groups react simultaneously. Although we have only investigated the 3-carboxypropyl-indoles **1a**,**b** until now,[8] it is apparent from our previous work[3] on indole-5-methanesulfonic acids, that this peculiar behavior of the sulfo group is not affected by the indole-3-substituent.

The regioselective synthesis of 4- or 6-substituted indoles as reactive synthetic intermediates is an important aspect in the chemistry of this heterocycle. Due to the enormous interest in ergot alkaloids a significant amount of work has appeared dealing with 3,4-disubstituted indoles[9] also present in the antibiotic nosiheptide.[10] The 4-vinyl-6,7-(dihydroxy)indole-2-carboxylates are key intermediates for the synthesis of the antitumor agent CC-1065 and of the inhibitors of cyclic adenosine-3′,5′-monophosphate phosphodiesterase PDE-I and PDE-II.[11] Indoles substituted at the 6-position are also important intermediates for the synthesis of a wide range of indolic alkaloids, such as members of the neoechinulin[12] and teleocidine[13] families.

The synthesis of indoles **1a**,**b** was accomplished through Fischer-type indolization of the hydrazone **10** obtained by the Japp–Klingemann procedure from diazotized (3-aminophenyl)methanesulfonic acid[14] **8** and ethyl 2-cyclohexanonecarboxylate **9** (Scheme 2). The Fischer synthesis starting from *meta*-substituted phenylhydrazones usually leads to the formation of 4- and 6-substituted indoles. The formation of mixtures of regioisomers can be avoided by blocking the appropri-



Scheme 2.

ate *ortho*-position of the phenylhydrazone with Cl or Br which is then removed from the indole by hydrogenolysis.[15] In our case the two regioisomeric indoles **1a**,**b** were produced in a 1:1 ratio and were easily separated by fractional crystallization from water in good overall yield (70%) as **1a** has much less solubility in polar solvents than **1b**. As the sulfonic acids or their salts possess very good crystallization properties the easy separation of the regioisomers is an important feature of the above process.

Another advantage related to our process is that the sulfo group of **1a**,**b**, as one of the chemically most stable functional groups, allows for a broad range of transformations of the indole nucleus. The chloromethyl functionality can then be introduced under mild conditions.

In summary, a new synthesis of 4- and 6-(chloromethyl)indoles featuring the transformation of the CH_2SO_3H group to CH_2Cl has been developed. The fact that the position of the sulfomethyl group does not play an important role in the loss of SO_2 suggests that the resonance interaction may not be the governing factor in this process. To reveal the exact nature, this desulfination process needs further investigation.

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6. General procedure for **7a** or **7b**: the appropriate sulfonate salt (**1a** or **1b**, 0.407 g, 0.1 mmol) was stirred in CH_2Cl_2 (25 ml) containing $SOCl_2$ (1 ml, 14 mmol) and DMF (0.06 ml) at rt for 4 h and then the solution was evaporated to dryness. The solid residue (**2a** or **2b**) was dissolved in MeOH, left for 10 min at rt then rotary evaporated to give **3a** (95%) or **3b** (92%) as white crystalline solids. The solution of **3a** or **3b** (0.34 g, 0.1 mmol, in CH_2Cl_2 (12 ml)) was added dropwise to Me_2NH solution (1 ml, 35% in H_2O) at 0°C while stirring. After 10 min at 0°C the organic phase was separated and evaporated to dryness to give **7a** (88%, mp: 82–83°C) or **7b** (95%, mp: 92–93°C).
7. ^1H NMR data (250 MHz, in $CDCl_3$) for **7a** and **7b**: **7a**: δ 1.40 (3H, t, $J=7$ Hz), 1.98 (2H, m), 2.24 (6H, s), 2.45 (2H, m), 3.36 (2H, m), 3.65 (3H, s), 3.68 (2H, s), 4.39 (2H, q, $J=7$ Hz), 6.96 (1H, d, $J=8$ Hz), 7.21 (1H, t, $J=8$ Hz), 7.26 (1H, d, $J=8$ Hz), 8.78 (1H, s). **7b**: δ 1.41 (3H, t, $J=7$ Hz), 2.01 (2H, m), 2.30 (6H, s), 2.36 (2H, m), 3.14 (2H, m), 3.57 (2H, s), 3.63 (3H, s), 4.39 (2H, q, $J=7$ Hz), 7.09 (1H, d, $J=8.3$ Hz), 7.35 (1H, s), 7.61 (1H, d, $J=8.3$ Hz), 8.83 (1H, s).
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