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Preparation of an *N-sec*-alkyl 2,6-disubstituted aniline: a key intermediate in the divergent synthesis of *S*-Metolachlor metabolites

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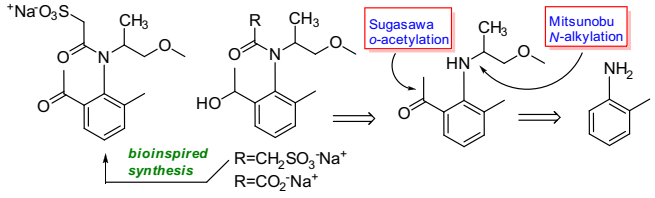
ABSTRACT

A simple method to prepare a 2,6-disubstituted aniline containing a *N-sec*-alkyl group and a carbonyl on one *ortho* substituent is reported. This method was used to accomplish the first synthesis of side chain oxidized ethylsulfonic acid (ESA) and oxanilic acid (OXA) metabolites of *S*-Metolachlor (*S*-Moc) herbicide. The 2,6-disubstituted aniline functionality was installed by a Sugasawa reaction of readily available *ortho*-toluidine. The *N-sec* alkyl group was introduced by a Mitsunobu alkylation of the nosyl-activated 2-acetyl-6-methyl-substituted aniline. This crucial step enabled access to the key 2,6-disubstituted aniline intermediate which was used in the divergent synthesis of *S*-Moc metabolites. A bioinspired synthesis of the keto-ESA metabolite was achieved in one step from the hydroxyl-ESA metabolite using a ruthenium-catalyzed oxidation.



Introduction

Effective weed control is an essential factor in high yield agriculture needed to feed the world's rising population. Metolachlor (**1**), an important member of the chloroacetamide class of herbicides, is used as a selective, pre-emergence herbicide to control a broad spectrum of grass weeds and small-seeded broadleaves (Fig. 1).[1,2] The molecule contains a stereocenter and a chiral axis due to hindered rotation around the phenyl-*N* bond axis (atropisomerism) thus leading to four stereoisomers (Fig. 1).[3,4] Metolachlor was initially launched as a mixture of all the four stereoisomers but it was later established that the majority of the herbicidal activity of the *racemic* Metolachlor was due to the 1′*S* enantiomer (α*R*,1′*S* and α*S*,1′*S* atropisomers).[5] It is noteworthy that both α*R*,1′*S* and α*S*,1′*S* atropisomers display identical herbicidal activity. Hence, an enantioenriched form of Metolachlor containing a mixture of 80–100% of 1′*S* and 0–20% of 1′*R* isomers was subsequently introduced in the market. This blend is currently named as *S*-Metolachlor (*S*-Moc) and is commercially available as Dual Magnum® herbicide. *S*-Moc is mainly taken up through the roots and shoots of the germinating plants and seedlings, leading to the eradication of the weeds before emergence.[6,7] Mechanistically, *S*-Moc is believed to reduce the formation of very-long-chain fatty acids (VLCFA) in the plasma membrane and epicuticular waxes of weeds by inhibition of fatty acid elongases.[8,9]

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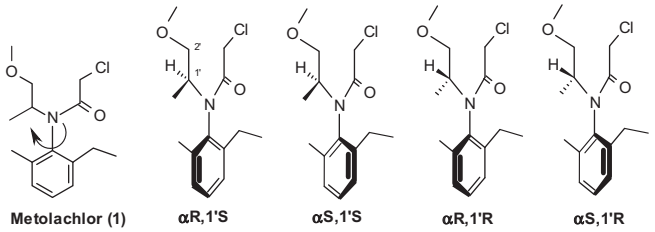


Figure 1. Structures of Metolachlor (**1**) and the individual stereoisomers.

The metabolism of Metolachlor/*S*-Moc has been studied extensively and is the subject of several publications.[10a–e] During the course of product re-registration, we identified side chain oxidized ethylsulfonic acid (ESA) metabolites **2** and **3** and oxanilic acid (OXA) metabolite **4** of *S*-Moc (Fig. 2). Since these metabolites had not been observed previously, we needed to prepare standards to support additional product registration requirements. The only available methods to obtain side chain oxidized ESA and OXA metabolites of *S*-Moc have hitherto been on analytical scale (with low yields) using microbial transformations.[10d,e] In this report, we describe our efforts to develop a synthesis that would generate all the stereoisomers of metabolites **2**–**4** since the technical *S*-Moc contains 80–100% of the *S* and 0–20% of the *R* isomers.

Results and discussion

Important structural features of **2**–**4** include the presence of an *ortho*-disubstitution arrangement, an oxidized ethyl side chain, an *N-sec* alkyl group, and highly polar functionalities (Fig. 3). The presence of two stereocenters coupled with a restricted rotation around the phenyl-*N* bond axis (atropisomerism) results in the formation of eight stereoisomers of metabolites **2** and **4**. Literature reports describing the synthesis of such densely functionalized anilines consisting of contiguous substituents are rare. We found only a limited number of reports describing preparation of 2-carbonyl-substituted anilines functionalized with *primary* *N*-alkyl[11] or *secondary* *N*-alkyl (isopropyl, methylpiperidine, and diethylaminoethyl)[11e,12,13] groups on the aniline nitrogen. To the best of our knowledge, there are no known methods for the synthesis of 2-carbonyl-6-alkyl-substituted anilines functionalized with *secondary* *N*-alkyl groups.

We envisioned that the most efficient method to synthesize the biosynthetically similar metabolites **2**–**4** would be from the 2-acetyl-6-methyl-substituted aniline **5**, using a divergent approach (Fig. 4). Aniline **5** contains the *N-sec*-alkyl group and a functional oxidation state of the ethyl side chain. With these key functionalities in place, we reasoned that the synthesis of metabolites **2**–**4** could be completed in 2–3 steps. Intermediate **5** could be synthesized either (i) in one step by installation of the *ortho*-carbonyl on to the *N-sec*-alkyl-substituted aniline **6** or (ii) via the introduction of the *N-sec*-alkyl group on to 2-carbonyl-6-methyl-substituted substrates **7** (Fig. 4).

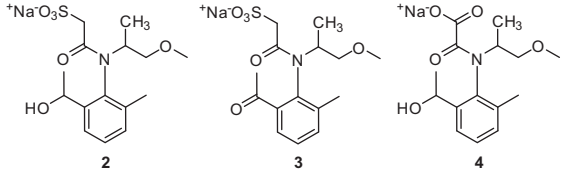


Figure 2. ESA and OXA metabolites **2**–**4** of *S*-Moc.

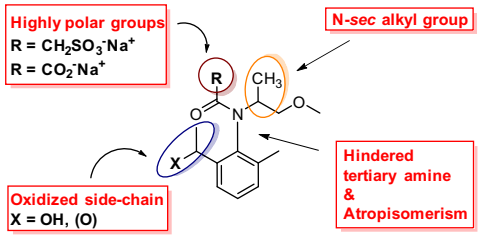


Figure 3. Structural features of metabolites **2**–**4**.

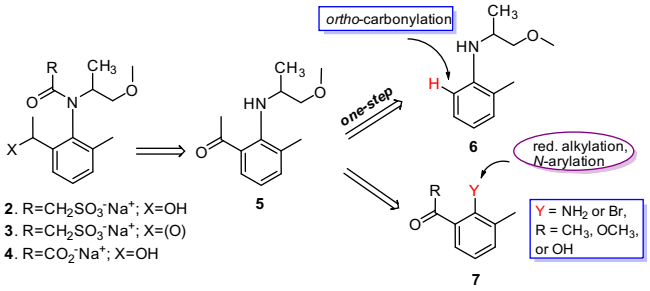
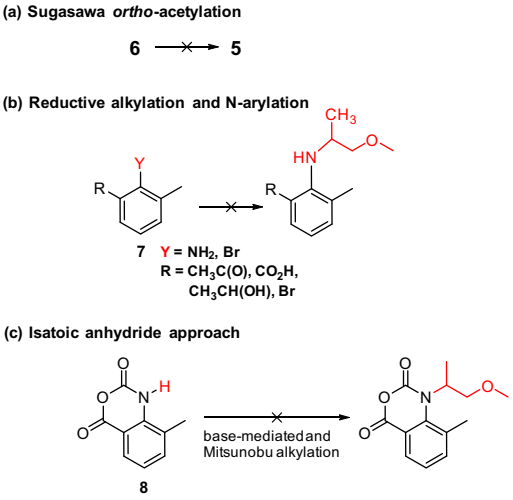


Figure 4. Retrosynthetic approach to metabolites **2**–**4**.

Synthesis of intermediate 5

We initially attempted to synthesize **5** via a one-step, Sugasawa *ortho*-acetylation of **6** (Scheme 1a) but isolated a mixture consisting of *ortho*-toluidine, *N*-(1-chloropropan-2-yl)-2-methyl aniline, and 2,7-dimethylindoline side products. Although the Sugasawa reaction has been demonstrated only on a limited number of *meta*- and *para*-substituted *primary*[11e] and *secondary*[13] anilines, the Lewis acids (BCl_3 and $GaCl_3$) in this reaction are incompatible with the *N-sec*-alkyl functionality in **6**. We next tested a variety of reductive alkylation[3,14] and Pd- and Cu-catalyzed *N*-arylation[15] conditions to install the *N-sec*-alkyl group on substrates **7** (Scheme 1b). However, our efforts resulted in a recovery of either starting material, debromination, isolation of trace amounts of product, and/or a complex mixture.[16] We also attempted to synthesize **5** via isatoic anhydride **8** since *N*-alkylated isatoic anhydrides serve as attractive latent precursors to *N*-alkylated anthranilates and anthranilic acids (Scheme 1c).[17] This approach also proved unsuccessful due



Scheme 1. Attempted approaches to synthesis of **5**.

to our inability to *N*-alkylate the isatoic anhydride **8** by either a Mitsunobu reaction (using 1-methoxy-2-propanol) or via alkylation methods (using 2-methoxy-1-methyl-ethyl-triflate) under basic conditions.[15d,18,19] While the efforts described above are effective methodologies for introducing *primary* alkyl substituents in substrates **7** and **8**, such methods were rendered ineffective for *secondary* alkyl substituents.

After several unsuccessful attempts to introduce the *N-sec* alkyl group, we finally pursued a strategy that involved alkylation of an activated aniline **9** (Fig. 5). To test our synthesis plan via **9**, we first performed an *ortho*-acetylation of *ortho*-toluidine (**10**) using a modified Sugasawa reaction[20] (by replacement of $AlCl_3$ with $GaCl_3$) to obtain **11**[21] in 88% yield (Scheme 2). Our next step was to determine a suitable activating group to facilitate an alkylation reaction. After a few trials,[22] a nosyl group activation of the aniline **11** was carried out using 2-nitrobenzensulfonyl chloride to obtain the *ortho*-nosyl-protected intermediate **12**.[23] We were delighted to achieve a Mitsunobu reaction of **12** with 1-methoxy-2-propanol[24] using PPh_3 and DIAD to afford the desired *N*-alkylated derivative **13** in 90% purified yield (Scheme 2).[23] Finally, deprotection of the nosyl group was accomplished using thiophenol and K_2CO_3 to form the desired key intermediate **5**.[23]

Synthesis of metabolites 2–4

Having secured intermediate **5**, we set our sights on completing the synthesis of metabolites **2**–**4**. Reduction of the carbonyl group in **5** was achieved using $NaBH_4$ to afford the desired secondary alcohol **14** as an approximately 1:1 mixture of diastereomers (Scheme 3).[25] Our momentum was however impeded in the next step due to the inability to selectively *N*-acylate intermediate **14** to form **15**.[26] We attempted to circumvent this issue by preparing intermediate **16** followed by a reduction of the carbonyl group in intermediate **16** using sodium borohydride. However, our efforts resulted in the formation of cyclized side product **17** instead of the desired product **15** (Scheme 3). After some experimentation, we settled on pursuing a strategy of diacylating intermediate **14** followed by a selective cleavage of the *O*-acyl linkage (Scheme 4). Thus, diacylation of **14** using 5 equiv of chloroacetyl chloride yielded the diacylated intermediate **18** as atropisomers of both the diastereomers. Selective cleavage of the *O*-acyl linkage in **18** was achieved by $Ti(OiPr)_4$ to form the desired *N*-acylated intermediate **15** as mostly a single atropisomer of both the diastereomers. Finally, the sulfonic acid functionality was introduced by the reaction of **15** with sodium sulfite and catalytic KI to form the sodium salt of the metabolite **2**. Our initial attempts to purify the metabolite **2** in the free sulfonic acid form using either preparative reverse phase (RP) or conventional normal phase flash purification methods (diol silica) were unsuccessful and resulted in partial decomposition of the product. However, we were able to purify **2** as a sodium salt by flash chromatography on a RP polar end-capped C18 stationary phase to afford the purified product in 72% yield as a diastereomeric mixture with both having atropisomers.

The synthesis of metabolite **4** was pursued by diacylation of **14** using 5 equiv of ethyloxalyl chloride to afford intermediate **19** in 79% purified yield as a mixture of four diastereomers (Scheme 5).

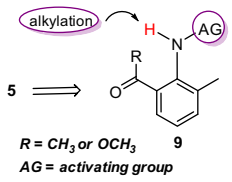
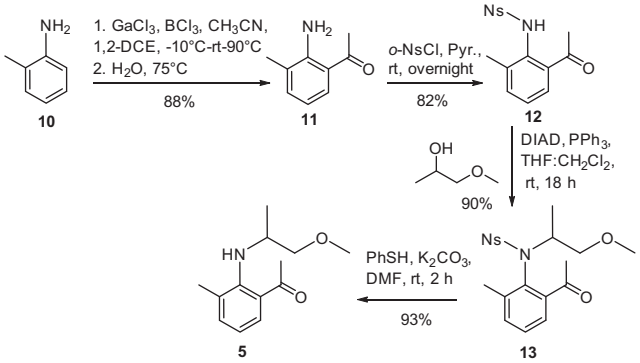
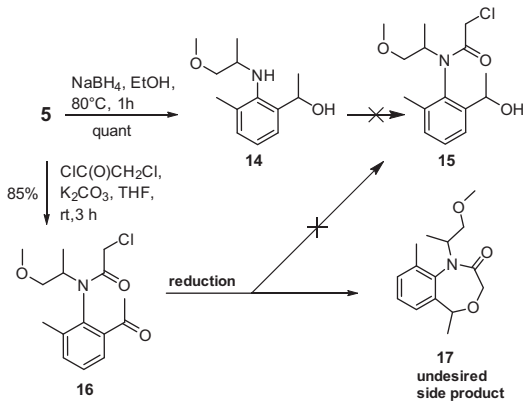


Figure 5. N-alkylation of an activated aniline.



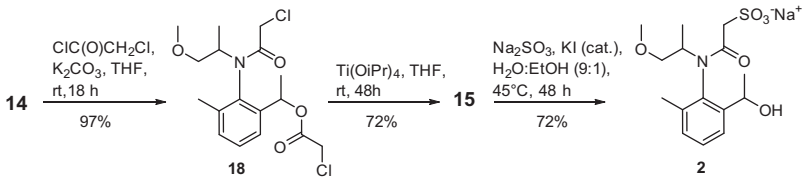
Scheme 2. Synthesis of intermediate **5** by a Mitsunobu alkylation of nosyl-activated aniline.



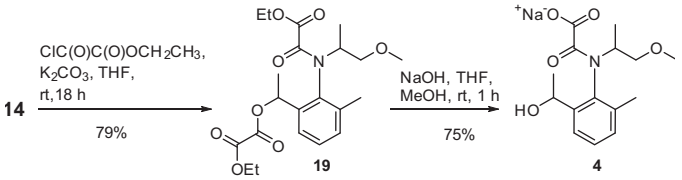
Scheme 3. Attempted synthesis of metabolite **2**.

A one-pot, in situ cleavage of the *O*-acyl linkage and hydrolysis of the ester in **19** afforded the desired sodium salt of metabolite **4** in 75% yield as a mixture of four diastereomers. Due to inherent instability and foreseeable challenges in purification of the free acid form, we purified metabolite **4** also as a sodium salt using a RP polar end-capped C18 stationary phase.

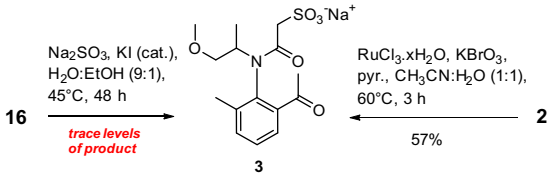
Having completed the synthesis of metabolites **2** and **4**, we then pursued the synthesis of metabolite **3**. Nucleophilic displacement of the chloride in **16** by Na_2SO_3 surprisingly afforded a complex mixture, containing only approximately 20% product (Scheme 6). Multiple attempts to purify this mixture to isolate the pure product (in >95% purity) were unsuccessful. We next considered a one-step bioinspired oxidation of metabolite **2** to **3** under aqueous conditions. Considering our limitations for oxidizing **2** in its salt form (due to the instability of the free acid form), we needed to employ aqueous non-acidic reaction conditions. We were specifically drawn to a report by DuBois and co-workers, describing the use of catalytic $RuCl_3$ and $KBrO_3$ to oxidize tertiary C–H bonds under aqueous neutral conditions.[27,28] Due to the low redox potential of 2° alcohols, we surmised that such mild reaction conditions could also be used in the oxidation of metabolite **2** to **3** with high chemoselectivity. Thus, we tested the oxidation of **2** using 10 mol % $RuCl_3$, 10 mol % pyridine, and $KBrO_3$ as stoichiometric oxidant in water:CH_3CN (1:1) as the solvent (Scheme 6). We were pleased to achieve a full conversion of metabolite **2** to the desired product **3** with high level of chemoselectivity. The purified product was isolated in 57% yield as an approximately 1:1 mixture of diastereomers. We observed approximately 5% of the over oxidized side product resulting from the oxidation of the benzylic methyl at the 6-position to form the corresponding aldehyde.



Scheme 4. Completion of the synthesis of metabolite **2**.



Scheme 5. Completion of the synthesis of metabolite **4**.



Scheme 6. Bioinspired synthesis of metabolite **3**.

Conclusions

In summary, the first high yielding synthesis of polar and sterically hindered ESA and OXA metabolites of *S*-Moc has been achieved. Furthermore, a simple method for the synthesis of an *N-sec*-alkyl 2-acetyl-6-methyl-substituted aniline is also reported. The synthesis of such class of anilines had hitherto been elusive. Pivotal to the success of our synthesis was the incorporation of the *sec* alkyl group via a Mitsunobu reaction of the nosyl-activated *ortho*-carbonylated aniline. This method offers a convenient means to introduce a *sec* alkyl group on to 2-carbonyl-6-alkyl-substituted anilines. A one-step, bioinspired synthesis of the keto-ESA metabolite was accomplished from the hydroxyl-ESA metabolite using a Ru-catalyzed oxidation. Our synthetic approach was dictated by the need to prepare test substances containing all the stereoisomers that could form metabolically from the technical *S*-Moc. However, a stereoselective synthesis of individual isomers could also be achieved using the synthetic route reported in this work.

Acknowledgements

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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.2016.10.077.

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25. The diastereomeric ratio for all the isolated compounds, including **14** were quantified by the integration values of the resolved resonances (of a particular proton environment) in the ^{1}H NMR spectrum.

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