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A high yielding synthesis of anthranilate esters from sterically hindered alcohols

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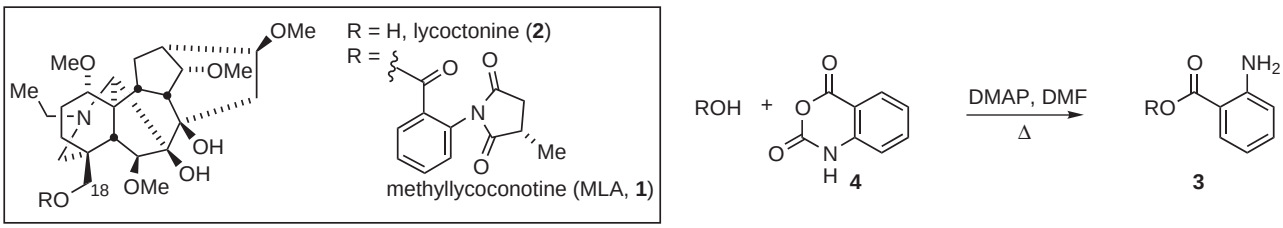
Abstract—A high yielding and operationally simple synthesis of anthranilate esters derived from primary, secondary and tertiary alcohols is reported. Esterification of the alcohol with *N*-(trifluoroacetyl)anthranilic acid under Steglich conditions, followed by sodium borohydride mediated cleavage of the trifluoroacetyl group affords the anthranilate ester. This new method has application in the synthesis of the ester sidechains of the commonly occurring *Delphinium* and *Aconitum* alkaloids and their analogues.

Diterpenoid alkaloids derived from *Delphinium* and *Aconitum* species constitute a structurally diverse class of biologically active natural products with a long history of use as medicines, poisons and insecticides.[1] A strong determinant of the biological activity associated with these alkaloids is the presence of an anthranilate ester sidechain, or its *N*-substituted derivatives, linked to the C-18 hydroxyl of the alkaloid skeleton. A dramatic example of the importance of this structural unit for biological activity is given by comparison of methyllycaconitine (**1**, MLA)[2] and its parent alkaloid lycoctonine **2** (Scheme 1). In competitive ligand binding studies at neuronal nicotinic acetylcholine receptors, MLA **1**, containing the 2-(2′-methylsuccinimido)benzoate ester sidechain, displays ca. 10^3 times more potent inhibition of α-bungarotoxin binding than its unsubstituted counterpart, **2**.[3] In fact, MLA is among the most potent, competitive small molecule antagonists of the α7-nicotinic acetylcholine receptor known.[4]

It has been proposed[5] that the tertiary amine and anthranilate ester sidechain of MLA **1** form an acylated homocholine structural array at physiological pH that gives rise to the potent nicotinic acetylcholine receptor binding. The pivotal nature of this sidechain and the paucity of efficient procedures for its synthesis lead us to disclose our recently developed procedure for the introduction of this structural unit.

The most common direct method for the synthesis of anthranilate esters like **3** (Scheme 1) is the reaction of an alcohol with isatoic anhydride **4** and catalytic base at elevated temperature.[6] The reaction is reported to proceed readily and in high yield (>95%) for unhindered primary alcohols, with difficulty for secondary



Scheme 1.

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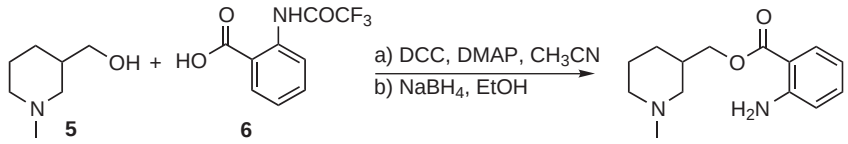
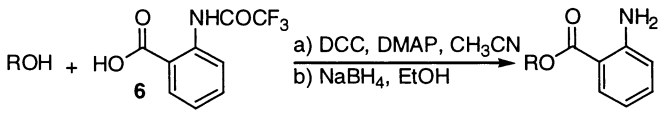
alcohols, giving mixtures of the desired ester and undesired isomeric carbamate by-product, and to fail completely in the case of tertiary alcohols.

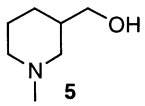
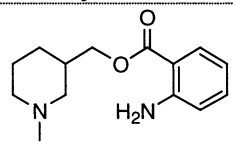
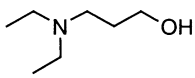
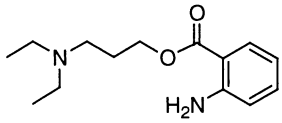
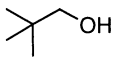
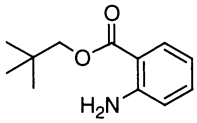
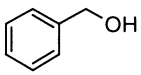
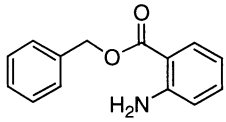
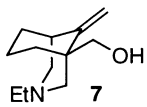
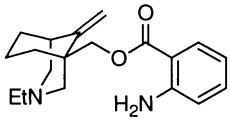
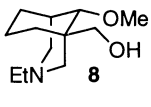
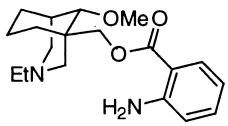
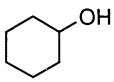
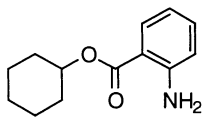
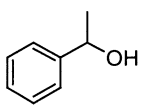
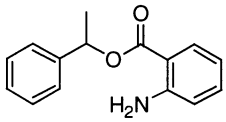
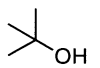
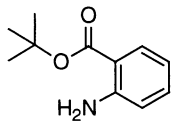
These conditions have been developed by Blagbrough[5] and adopted by other workers for the synthesis of MLA analogues.[7,8] In general, low yields (typically



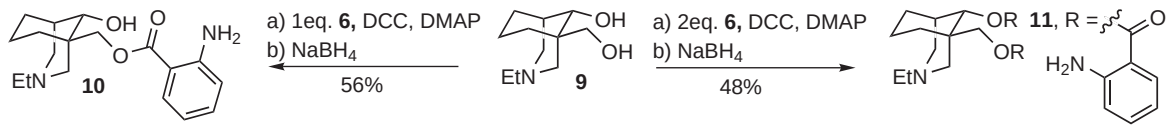
Scheme 2.

Table 1. Synthesis of anthranilate esters with *N*-(trifluoroacetyl)anthranilic acid **6**



entry	alcohol	product	yield of ester (%)[a]
1			81 (72)[b,c]
2			85 (75)[b,c]
3			94 (64)[b,d]
4			85 (90)[b,e]
5			75 (40)[b,c]
6			83 (65)[b,d]
7			97 (16)[b,c]
8			91
9			39 (77)[f]

[a] Yield of anthranilate ester prepared by alternative literature based methods in parentheses. [b] Prepared by reaction with isatoic anhydride. [c] Prepared according to ref. 6b. [d] See ref. 5. [e] See ref. 6b. [f] See ref. 10.



Scheme 3.

40–65%) of the desired anthranilate esters are obtained which can be attributed to the hindered neopentyl environment of the C-18 hydroxyl group present in lycoctonine and many simpler analogues. The low yields of ester formation by these methods have prompted investigations into the introduction of this sidechain by alternative procedures,[7,8a,9] however, none of these methods has offered a general and high yielding solution to the problem of sidechain introduction.

In connection with our studies towards MLA analogues, we turned our attention to the coupling procedure developed by Breslow[10] as an alternative to the isatoic anhydride mediated synthesis. Initial attempts to repeat this coupling procedure on stoichiometric quantities of the alkoxide salt derived from 1-methyl-3-piperidinemethanol (**5**, Scheme 2) did not result in practical yields of the coupled product. However, reaction of **5** with three equivalents of *N*-(trifluoroacetyl)anthranilic acid **6** under Steglich conditions[11] (DCC/DMAP) followed directly by sodium borohydride mediated cleavage of the crude amide gave a gratifying 81% yield of the anthranilate ester.[12,13] This compares favourably with the base catalysed reaction of isatoic anhydride, which in our hands proceeded in 72% yield (Table 1, entry 1).[6b] This high yielding and operationally simple anthranilate ester synthesis prompted us to explore the scope of this coupling reaction as an alternative to conventional approaches.

The reaction of a range of simple primary alcohols with **6** afforded good yields of the anthranilate esters in comparison with the isatoic anhydride mediated synthesis (Table 1, entries 2, 3 and 4). Extension of this procedure to AE bicyclic analogues of MLA, **7** and **8**[5d] (Table 1, entries 5 and 6) containing neopentyl substituted alcohols also afforded coupled product in improved yield.

Secondary alcohols were observed to react readily with **6** to afford high yields of the anthranilate ester (Table 1, entries 7 and 8). To our knowledge this procedure represents the first direct, high yielding synthesis of anthranilate esters derived from secondary alcohols reported in the literature.[6] Attempts to promote the esterification of tertiary alcohols, however, afforded lower yields of the coupled product, in line with the synthesis of *t*-butyl benzoate ester derivatives initially reported by Steglich.[11] The use of di-2-pyridyl thiocarbonate,[14] recently recommended for the synthesis of esters derived from tertiary alcohols failed to give the desired product.

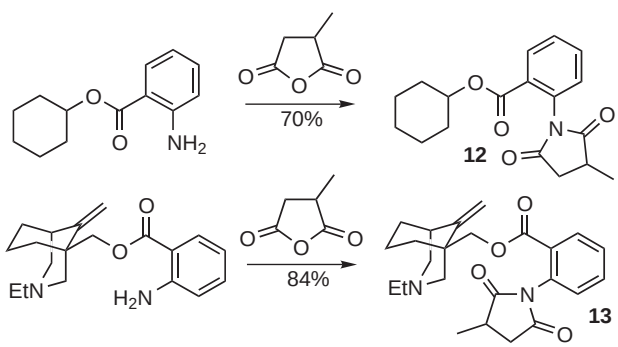
The extreme conditions associated with the isatoic anhydride mediated synthesis of anthranilate esters have been reported to lead to poor regioselectivity or possibly transesterification during reactions with diol substrates.[5a] We therefore investigated the new procedure to assess its potential for kinetic discrimination leading to the selective esterification of diol substrates (Scheme 3). To this end the reaction of bicyclic diol **9** with one equivalent of acid **6** favoured reaction at the primary hydroxyl to give selective mono-anthranilate ester **10** in 56% yield, together with a small quantity of the diester **11** (10%). Reaction of **9** with 2 equivalents of acid gave the diester **11** in a moderate 48% yield.

Finally, heating the anthranilate esters with 2 equivalents of 2-methylsuccinic acid at 125°C according to the procedure of Blagbrough[5c] cleanly afforded the succinimide derivatives **12** and **13** in good yield (Scheme 4). This procedure therefore offers a simple two-step method for the introduction of the 2-(2′-methylsuccinimido)benzoate ester sidechain present in methyllycaconitine **1** and other delphinium alkaloids.

In conclusion, we have developed a practical, high yielding synthesis of anthranilate esters from primary and secondary alcohols using *N*-(trifluoroacetyl)anthranilic acid **6**. The reactions proceed under mild conditions and offer a practical alternative to existing procedures. This method should find wide applicability for the synthesis of diterpenoid alkaloids such as methyllycaconitine and their analogues. Synthetic studies and biological activity data will be reported in due course.

Acknowledgements

Generous financial assistance from Dunlena Pty. Ltd and an Australian Postgraduate Award (Industry) to D.B. (C29804582) supported this work.



Scheme 4.

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12. Standard procedure: To a solution of alcohol (1 mmol), *N*-(trifluoroacetyl)anthranilic acid **6** (2 mmol) and 4-dimethylaminopyridine (0.1 mmol) in acetonitrile (5 ml) was added dicyclohexylcarbodiimide (2 mmol) and the mixture stirred, under an atmosphere of nitrogen, at 40°C for 24 h. After this time the mixture was cooled, filtered and the filtrate evaporated to dryness. The crude reaction mixture was then dissolved in dichloromethane (20 ml), washed with aq. sodium bicarbonate (20 ml) and brine (20 ml), dried ($MgSO_4$) and concentrated in vacuo to leave the crude *N*-(trifluoroacetyl)anthranilate ester. This was suspended in absolute ethanol (10 ml), sodium borohydride (2 mmol) was added, and the mixture was stirred for 3 h. The reaction was quenched by the addition of water (5 ml) and the volatile solvent removed in vacuo. The remaining aqueous solution was then extracted with ethyl acetate (2×30 ml) and the organic layer washed with brine (50 ml), dried ($MgSO_4$) and concentrated in vacuo to leave the crude product which was purified by flash chromatography to afford the anthranilate ester.
13. All compounds gave satisfactory ^1H, ^{13}C NMR, IR and MS data.
14. Saitoh, K.; Shiina, I.; Mukaiyama, T. *Chem. Lett.* **1998**, *7*, 679. In our hands the di-2-pyridyl thiocarbonate mediated esterification of 3-phenylpropionic acid with cyclohexanol gave cyclohexyl 3-phenylpropionate in 92%, which compares favourably with the literature reported yield of 96%.