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Syntheses of spiro[cyclopropane-1,3'-oxindole]-2-carboxylic acid and cyclopropa[c]quinoline-7b-carboxylic acid and their derivatives

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Abstract
The synthesis of spiro[cyclopropane-1,3'-oxindole]-2-carboxylic acid, including novel 3-(2- and 3-pyridyl)-substituted analogues and the novel cyclopropa[c]quinoline-7b-carboxylic acid and their ester and amide derivatives is described. These syntheses involve diastereoselective cyclopropanation reactions of methyl 2-(2-nitrophenyl)acrylate and (3E)-(pyridin-2-ylmethylene)- and (3E)-(pyridin-3-ylmethylene)-1,3-dihydro-2H-indol-2-one with ethyl (dimethyl sulfanylidene) acetate (EDSA). The synthesis of methyl cyclopropa[c]quinoline-7b-carboxylate involves a regioselective reductive cyclization of a nitro-diester precursor. The relative stereochemistry of key compounds has been determined by single-crystal X-ray structural analysis.

Keywords
Syntheses, spiro, cyclopropane, oxindole, carboxylic, acid, cyclopropa, quinoline, carboxylic, acid, their, derivatives, CMMB

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Synthesis of spiro[cyclopropane-1,3’oxindole]-2-carboxylic acid and cyclopropa[c]quinoline-7b-carboxylic acid derivatives

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Abstract: The phosphine-catalysed [3+2]-cycloaddition of the 2-methylene \(\gamma\)-lactams \(4\) and \(5\) and the acrylate \(6\) with the ylides derived from the ethyl ester, the amide or the chiral camphor sultam derivative of 2-butyenoic acid (\(7\text{a-c}\)) give directly, or indirectly after reductive cyclization, spiro-heterocyclic products. The acid \(32\) underwent Curtius rearrangement and then acid hydrolysis to give two novel spiro-cyclic ketones, \(41\) and \(42\).

Key words: cyclopropanation, sulfur ylide, spirocyclic compounds, oxindole

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1. Introduction

3’,Spirocyclo-oxindoles, of synthetic or natural origin, have a range of biological activities.\textsuperscript{1-3} As part of a medicinal chemistry project we have been focusing on the synthesis of novel 3’-spirocyclo-oxindoles and we recently reported the preparation of 3’-spiropentacyclo-oxindoles derivatives using phosphine-catalyzed [3+2]-cycloaddition reactions.\textsuperscript{4} As an extension of this project we required the synthesis of 3’-spirocyclopropyloxindole-2-carboxylic acid \(1\) and cyclopropa[c]quinoline-7b-carboxylic acid \(3\) and their ester and benzamide derivatives and the 3-(2- and 3-pyridyl)-substituted analogues (\(2\)) of \(1\).
During the course of this project He et al.\textsuperscript{4} reported that some ester and amide derivatives of the 5'-bromo-3'-spirocyclopropyloxindole-2-carboxylic acid 4 (R = OH, Y = Br) were potent HIV-1 non-nucleoside reverse transcriptase inhibitors (NNRTIs) on both wild-type and drug resistant mutant viruses. The ethyl ester of compound 4 was prepared from the 3-carboethoxymethylene derivative of 5-bromoisatin (8, R = Br) by treatment with diazomethane to generate the cyclopropanated product, via its diazo intermediate. Similar reactions have been utilized earlier to prepare 2-substituted-3'-spirocyclopropyloxindole-2-carboxylic esters, however extension of these reactions to prepare 3-phenyl-3'-spirocyclopropyloxindole-2-carboxylic esters 5 using phenyldiazomethane were unsuccessful.\textsuperscript{5} Interestingly, when diphenyldiazomethane was employed the desired 3,3-diphenyl-3'-spirocyclopropyloxindole-2-carboxylic ester was obtained.\textsuperscript{6} In the same year Shanmugam reported the synthesis of N-alkyl derivatives of 4 (R = O-alkyl, X = H, Y = H or Br) employing a reductive cyclization reaction to prepare the cyclopropane ring.\textsuperscript{7} Indeed prior to the work disclosed here, no methods were available to prepare 3-aryl-3'-spirocyclopropyloxindole-2-carboxylic esters, including the desired 3-(2- and 3-pyridyl)-substituted analogues 2. Earlier work by Croce,\textsuperscript{8} however, showed that the related phenyl ketone derivatives, 6 and 7 could be prepared from the reaction of dimethylsulphonium phenacylide (Me\textsubscript{2}S(+)(CH(-))COPh) with 8 (R = H) or 3-methylene-indoline-2-one, respectively. The former products were formed as a mixture (1.5-3.5 : 1) of diastereomers.
In 2006 He et al.\textsuperscript{9} also disclosed that derivatives of the ethyl cyclopropa[c]quinoline-1c-carboxylate 9, closely related to our target structure 3, also had potent HIV antiviral activities as NNRTIs. We report here our own efforts for preparing 3'-spiropolyoxindole derivatives related to 1 and a method of preparing for the first time 3-aryl-substituted analogues 2 (X = 2- or 3-pyridyl) using stabilized sulfur ylides. Furthermore, we report an efficient and highly diastereoselective synthesis of cyclopropa[c]quinoline-7b-carboxylic acid 3, a new isomer of He’s compound 9.

2. Results and Discussion

The synthesis of the corresponding esters of 1 and 3, 13 and 12, respectively (Scheme 1) could in principle be achieved by regioselective reductive cyclization reactions of the nitro diester 11. Based on literature precedent of related but non-cyclopropylated nitro diesters, cyclization should favor formation of a quinoline ring system over an oxindole ring structure.\textsuperscript{10,11} However, at the onset of this study, the effect of the cyclopropane moiety in 11 on the regioselectivity of such a reductive cyclization reaction was not certain. The nitro-diester 11 was prepared in 80 \% yield in a completely diastereoselective fashion by treatment of the acrylate 4\textsuperscript{4,12} with ethyl (dimethyl sulfuranylidene) acetate (EDSA, 1.5 equiv) in anhydrous toluene for 20 h at rt. Single X-ray crystallographic analysis of 11 showed that the two polar ester groups had a \textit{trans}-stereochemical relationship (Figure 1). This stereochemical outcome was expected based on literature precedent of related reactions.\textsuperscript{13}
Figure 1 Single-crystal X-ray crystallographic structure of 11.
Reductive cyclization of 11 using zinc and HCl under refluxing conditions, led to the formation of the expected products, 12 and 13. This reaction was highly regioselective (12 : 13 = 12 : 1) in favour of the formation of the quinoline 12 over the indolone 13. In contrast, catalytic hydrogenation of 11 using Pd/C and H2 led to a less regioselective reaction providing a 4 : 1 ratio.
mixture of 12 and 13, in favour of the quinoline product 12. The higher regioselectivity found in the former method may be due to Zn$^{2+}$ activation of the less hindered ester carbonyl by coordination, leading to more of the quinoline product 12. Compounds 12 and 13 were readily separated by column chromatography and their structures were established by single-crystal X-ray crystallographic analysis (Figure 2). The $^1$H NMR spectral data of 13 at 300 MHz was similar to that reported in 1978 by Bennet$^5$ for the same compound at 60 MHz. We thus we assume that the same diastereomeric compound was produced from these two different synthetic routes. Furthermore, the $^1$H NMR spectral data for the cyclopropane resonances of 13 matched very closely to the analogous N-methyl analogue of 13 that was recently reported.$^7$ Saponification of 12 and 13 gave the carboxylic acids, 3 and 1, respectively which were converted to their respective amide derivatives 14 and 15, under EDCI/HOBT coupling conditions with aniline.

![Figure 2 Single-crystal X-ray crystallographic structures of 12 (left) and 13 (right).](image)

A more direct method to synthesise the indolone amide 15, involved cyclopropanation of the acrylate 10 with the ylide derived from the sulfonium salt 19, which was readily prepared in three synthetic steps from chloroacetyl chloride 16, as outlined in Scheme 2. This ylide has been prepared previously from the reaction of dimethylsulfoxonium methylide and phenylisocyanate, however its subsequent reactions were not reported.$^{13}$ Although far less common than their ester-
sulfonium analogues, amide-sulfonium salts like 19 have been previously used for the cyclopropanation reactions of electron deficient alkenes, however normally as the secondary amide.\textsuperscript{14}

**Scheme 2\textsuperscript{a}** (Compounds 15 and 20 are racemic)

\[\begin{align*}
\text{Cl} & \quad \text{Cl} \\
16 & \quad \text{a) Cl} \\
\text{Cl} & \quad \text{O} \\
17 & \quad \text{b) b)} \\
\text{MeS} & \quad \text{O} \\
18 & \quad \text{c) MeS} \\
\text{HN} & \quad \text{N} \\
19 & \quad \text{d)} \\
\text{Me2S} & \quad \text{O} \\
19 & \quad \text{e) e)} \\
\end{align*}\]

\textsuperscript{a} Reagents and conditions: (a) Aniline (1.1 equiv), pyridine (1.5 equiv), anhydrous CH\textsubscript{2}Cl\textsubscript{2}, 0 °C→RT, 1 h, 74%; (b) MeSNa (1.1 equiv), anhydrous MeOH, RT, 15 min, 98%; (c) MeI (10 equiv), anhydrous CH\textsubscript{2}Cl\textsubscript{2}, RT, 2 d, 52%; (d) 10, 19 (1.5 equiv), DBU (1.1 equiv), anhydrous CH\textsubscript{2}Cl\textsubscript{2}, RT, 2 d, 39% (b) Fe (8 equiv), AcOH, EtOH, sonication, 2 h, 60%.

The cyclopropanation reaction of the acrylate 10 and the ylide generated \textit{in situ} from the sulfonium salt 19 (1.5 equiv) with DBU (1.1 equiv) in anhydrous DCM for 2 d at RT yielded solely the \textit{trans} product 20 in an unoptimised yield of 39%. The structure of 20 was unequivocally established by single-crystal X-ray structural analysis (Figure 3). The reductive cyclisation of 79, using the
methods described in Scheme 1, however were not productive. Previously it was found that cyclisation of indolones can proceed using iron with acetic acid under sonication. This method successfully yielded the desired product 75 in a yield of 60%.

Figure 3 Single-crystal X-ray crystallographic structure of 20.

For the preparation of target molecules 2, the α-methylene indolinones 53a and 53b were prepared according to the literature. Their E-geometries were unequivocally established by single-crystal X-ray structural analysis. The cyclopropanation of either 53a or 53b with EDSA in anhydrous acetonitrile for 24 h at RT yielded a mixture of three diastereomeric cyclopropanes products.

Scheme 3.1). For the reaction using 53a, 1H NMR analysis of the crude reaction mixture revealed a 5.6 : 1.8 : 1 mixture of the diastereomeric products, 81a, 82a and 83a, respectively. In contrast, the cyclopropanation reaction using 53b proved to be a much more diastereoselective reaction giving a 43 : 7 : 1 mixture of the diastereomeric products, 81b, 82b and 83b, respectively. Separation of these diastereomeric products by column chromatography proved difficult and only compounds 81a and 83a could be isolated diastereomerically pure in yields of 27% and 12% yields, respectively. The remaining chromatographic fractions consisted of mixtures of all three isomers. In contrast the
major trans isomer 81b, was readily isolated in diastereomERICally pure form in 61% yield from 53b. DiastereomERICally pure samples of the other isomers however, could not be obtained.

Scheme 3.1a (all compounds are racemic)

The structure of 81b was unequivocally established by single-crystal X-ray structural analysis (Figure 3.3). The assignment of the relative stereochemistries of the diastereomERIC products produced in Scheme 3 was based on the coupling constants observed for the cyclopropane methines, CH-3’ and CH-2’. The chemical shifts and coupling constants for the major isomers of both reactions (81a and 81b), and corresponding minor isomers according to prevalence ((82a and 82b) and (83a and 83b)) were almost identical, indicative of their same relative configurations. For the isomERIC set, 81a-83a the methine cyclopropane 1H NMR resonances appeared as doublets for all diastereomers, with one methine of the major isomer 81a having the most downfield signal (δ 3.93) and one at δ 3.46. For the isomer 83a both cyclopropane methines had very similar chemical shifts and appeared almost like an ABq (δ 3.86 and 3.82). While one methine for the isomer 82a had the most upfield signal (δ 3.08) and one at δ 3.57. The vicinal coupling constants for two of the
products, **81a** and **83a**, was found to be the same, $^{3}J \sim 8.1$ Hz. This was in contrast to isomer **82a**, which had a vicinal coupling constant of $^{3}J \sim 10$ Hz. Since in cyclopropanes, *cis*-vicinal coupling constants ($^{3}J \text{cis} (H_{\alpha}H_{\delta})$ 6-12 Hz) are usually larger than *trans*-vicinal coupling constants ($^{3}J \text{trans} (H_{\alpha}H_{\delta})$ 4-8 Hz)$^{12}$ the major diastereomer, **81a** and **81c** were assigned the 1,2-trans stereochemistries while the second most prominent isomer (**82a**) was the *cis* isomer.

![Figure 3.3](image)

**Figure 3.3** Single-crystal X-ray crystallographic analysis of **81a** (left) and **81b** (right).

Of the four possible racemic *anti* betaine intermediates involved in these reactions, the
In conclusion, the cyclopropanation reaction utilising sulfur ester and amide ylides has proven to be a good method of synthesising spirocyclopropane-1’,3-indoles. Compounds 53a, 53b, 81a, 81b and 83a were submitted for cytostaticity studies and protein inhibition studies and the results of these are discussed in Chapter 6.
a Reagents and conditions: (a)

Reagents and conditions: (a) K₂CO₃ (2 equiv), MeOH/H₂O, high pressure tube, 60°C, 5 h, 94%;
(b) Aniline or 4-N,N-dimethylaminoaniline (1.7 equiv), HOBt (1 equiv), EDCI (1 equiv), MeCN,
0°C→RT, 15 h, 92% (33a), 44% (33b).

3. Cytotoxicity Studies
Compounds 15, 25a,b, 27, 31, 33a,b, 41, 42, 43 and 44 were all tested for their cytotoxic activity
against the cancer cell lines H460 (human non small cell lung), MCF-7 (human breast) and SF-268
(human CNS) at the Peter MacCallum Cancer Centre, St Andrew’s Place, East Melbourne, Vic,
3002, Australia. Biological testing was performed using standard NCI procedures at a drug
centration of 25 μM (5 mM drug stocks were prepared in DMSO. Cells were then exposed to 25
μM of each drug for 72 h. The cells were then fixed, stained with SRB and the percentage cell
growth relative to the solvent control determined). Percent cell growth calculated from this testing showed little or no cytotoxic activity. The best activity was 50% cell growth at 25 μM for 33b against H460.

In conclusion, we have developed a new strategy for the synthesis of both racemic and enanti-enriched versions of the 2-azaspiro[4.4]nonan-1-one and spiro[cyclopentane-1,1′-[1H]isoindol]-3′(2′H)-one ring systems using the phosphine-catalysed [3+2]-cycloaddition of both ester (7a) and amide derivatives (7e) of 2-butyroic acid. Enantiomerically enriched versions of 2 can be obtained using a chiral (1S)-camphor sultam derivative 7b of 2-butyroic acid. We have also demonstrated the potential of these compounds as scaffolds for developing libraries of novel spiro-heterocyclic compounds.

4. Experimental

For X-ray structure determinations see supporting information. All 1H NMR spectra were performed at 300 MHz and all 13C NMR (DEPT) spectra at 75 MHz in CDCl3 solution, unless otherwise noted. Abbreviations: PS (petroleum spirit, bp 40-60°C) and DCM (dichloromethane).

5. References


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