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A novel and convenient access to highly substituted spiro[pyrrolidinon-3,3′-indoles]

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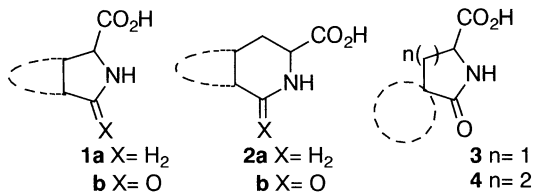
Abstract—2-Substituted indoles were reacted with benzaldehyde, Meldrum's acid and triethylamine, to give a trimolecular adduct, further leading to spiro[pyrrolidinon-3,3′-indoles]. © 2001 Elsevier Science Ltd. All rights reserved.

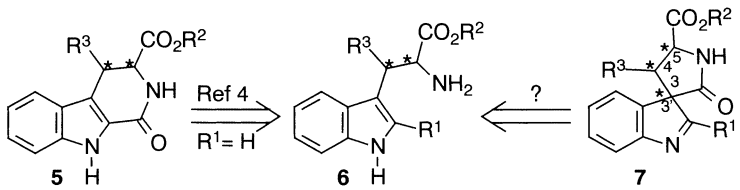
Synthesis of modified proline **1a** and pipecolic acid **2a** derivatives proved to be of interest in the search for potent excitatory amino acid receptor antagonists.[1] Their 2-oxo derivatives **1b** and **2b**, however, could be considered as constrained peptide analogues.



Less attention has been paid to spiro analogues **3** and **4**, which exhibit the same level of constraint although adopting an orthogonal geometry instead of a planar one for **1** and **2**. Moreover, the newly created stereocenter enables us to differentiate between forward and backward faces of the peptide-like moiety. Independent of their pharmacological interest, these type of molecules are attractive reactive intermediates toward powerful electrophile acyliminium systems by decarbonylation[2] or oxidative decarboxylation.[3]

Some years ago, we reported a convenient synthesis of 1-oxo-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid derivatives **5** starting from R^3-substituted tryptophan ester **6** ($R^1 = H$) and a phosgene equivalent,[4] we hypothesized that a similar approach could also be useful for the preparation of spiroindolenines **7** (Scheme 1). It needs to be emphasized that analogous spiro derivative syntheses have been recently published,[5] but none of them allows the simultaneous introduction of R^3, CO_2R^2 and oxo substituents on the pyrrolidine ring.

In this letter we disclose our preliminary results leading to functionalized spiro derivatives **7**. Initially, we adapted the Neef's synthesis of β-substituted tryptophan esters[6] to 2-thiomethylindole **8**. This latter smoothly reacted with the nitroester **9** giving a racemic [1:1] mixture of the (*R**,*S**) and (*S**,*S**) condensation products **10**, which was reduced by Pd/C into the tryptophan derivatives **11** in 25% yield from **8**. Unfortunately, none of the known procedures[7] gave rise to the isocyanate intermediate nor to the spiro derivative **7** (Scheme 2).



Scheme 1.

Keywords: indoles; isocyanates; spirocompounds.

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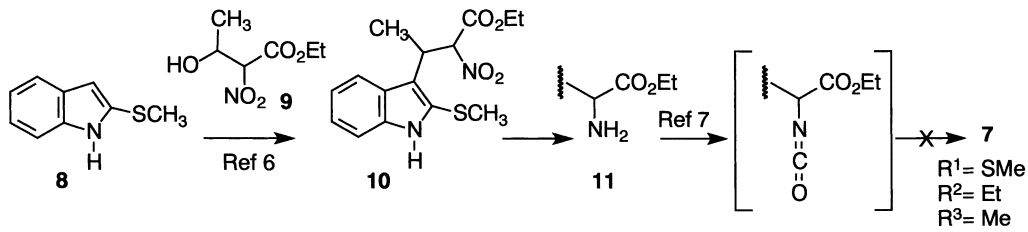


Scheme 2.

Thus, we turned our attention to another strategy exploiting our previously described synthesis of β-substituted tryptophan derivatives,[8] based on a three component reaction[9] between indole, aldehyde and Meldrum's acid (Scheme 3, $R^1 = H$).

Contrary to our expectations, the trimolecular condensation between a 2-substituted indole, benzaldehyde and Meldrum's acid, did not occur under the same conditions (cat. D,L-proline, heating in CH_3CN) as found with unsubstituted indole ($R^1 = H$). Finally, in the presence of one equivalent of triethylamine, 'trimolecular adduct salts' **14** could be obtained in good yield by simple filtration (see Table 1).[10] We already observed the formation of such a salt, by adding a stoichiometric amount of butylamine to trimolecular adducts **13**.[11] Transformation of **14** into acylazides was performed in two steps in agreement with our previous findings:[12] ring cleavage of the Meldrum's acid by *tert*-butanol, followed by diphenylphosphoryl azide (DPPA)-mediated acylazide formation. Non-isolated azides **16** were subjected to thermal rearrangement, followed by spirocyclization to afford an unseparable three compound mixture of isomers. To our knowledge, these are the first spiro[pyrrolidinon-3,3′-indolenine] derivatives ever synthesized with substituents at both positions 4 and 5.

Starting from ethyl 2-indolylacetate **12d**, the same transformations gave rise to the vinylogous urethane **19**, a possible intermediate toward Aspidosperma alkaloids[13] (Scheme 4).

Besides the expected acid esters, variable amounts (10–15%) of the tetramolecular adduct **18**,[14] during the solvolysis of **14d** by *tert*-butanol, was obtained resulting from the reversibility of the process and the presence of activated methylene protons.

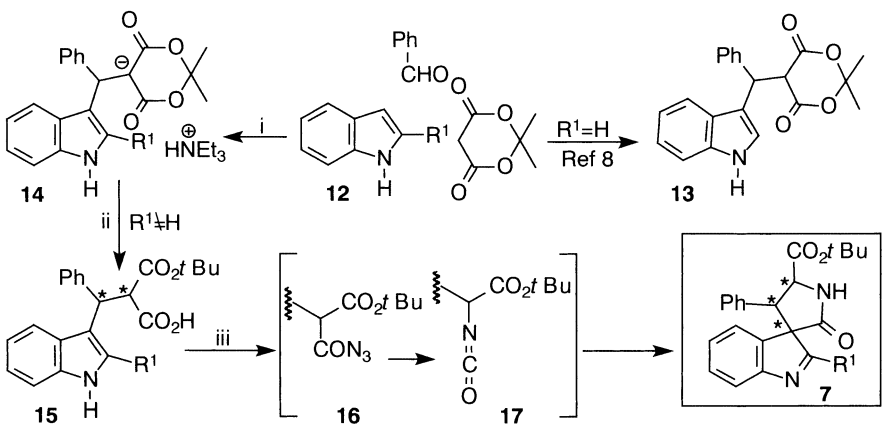
When the non-isolated azides **16** were subjected to thermal Curtius rearrangement in the presence of benzyl alcohol, nucleophilic attack of BnOH on isocyanates **17** could compete with spirocyclization, allowing the isolation of **7** or **19** (21–46% yields) and carbamate esters **20** (18–42% yields). Those compounds can be considered as orthogonally protected forms of new non-natural functionalized tryptophans **21** (Scheme 5).

It remains to be indicated that spiro derivatives **7** by heating to reflux in toluene and benzyl alcohol in the presence of triethylamine, could be transformed into **20**. This reaction demonstrates the unusual reactivity of this secondary amide towards nucleophile, as well as

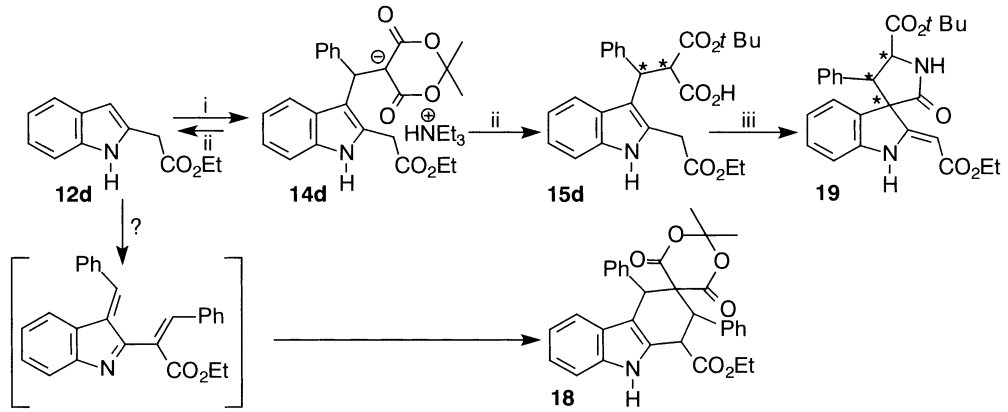
Table 1.

Entry		R^1	Yields (%)			
			14	**15**[a,b]	**7**[a,c]	**19**[a,c]
1	**a**	SCH_3	78	78	52	–
2	**b**	CH_3	60	70	63	–
3	**c**	Ph	71	40	42	–
4	**d**	CH_2CO_2Et	67	67	–	77

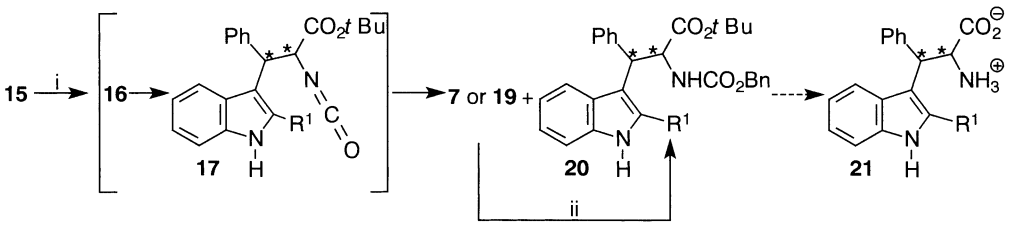
[a] Yield of isolated product after purification by column chromatography.
[b] Isomer ratio 1.5:1.
[c] Unseparable mixture of three isomers.



Scheme 3. *Reagents and conditions*: (i) Et_3N, CH_3CN, rt; (ii) *t*-BuOH, reflux; (iii) DPPA, Et_3N, toluene, 120°C.



Scheme 4. *Reagents and conditions*: (i) PhCHO, Meldrum's acid, Et_3N, CH_3CN, rt; (ii) *t*-BuOH, reflux; (iii) DPPA, Et_3N, toluene, 120°C.



Scheme 5. *Reagents and conditions*: (i) DPPA, Et_3N, toluene, 120°C, 1.5 h; then BnOH, 120°C, 1.5 h; (ii) Et_3N, BnOH, toluene, 120°C, 2 h.

the utility of spiro lactam **7** like an '*N*-selfprotected' form of amino acid **21**.

In conclusion, we have described a novel methodology which provides easy access to spiro[pyrrolidinon-3,3′-indoles], based on a domino acylazide formation–Curtius rearrangement–thermal intramolecular isocyanate spirocyclization process. Further studies extending this reaction to the preparation of natural product analogues are currently under investigation.

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10. All new compounds gave satisfactory spectral data. Compound **14a**: mp 139–141°C; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 10.90 (s, 1H), 7.55 (d, J=8.0 Hz, 1H), 7.21 (d, J=8.0 Hz, 1H), 7.14–7.08 (m, 1H), 7.01–7.00 (m, 1H), 6.98 (t, J=8.0 Hz, 1H), 6.70 (t, J=8.0 Hz, 1H), 5.77 (s, 1H), 2.92 (q, J=7.3 Hz, 6H), 2.37 (s, 3H), 1.46 (s, 6H), 1.08 (t, J=7.3 Hz, 9H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 165.3, 146.8, 136.9, 128.1, 127.8, 127.4, 126.9, 124.0, 123.0, 122.7, 120.6, 117.4, 110.0, 99.1, 76.9, 45.6, 38.1, 26.1, 18.3, 8.6; Anal. calcd for $C_{28}H_{36}N_2O_4S$: C, 67.71; H, 7.30; N, 5.64. Found C, 67.86; H, 7.61; N, 5.65.
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14. Obtained in a mixture of two diastereomers (4:1). Selected data for major isomer of **18**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.45 (s, 1H), 7.43–6.84 (m, 14H), 5.23 (d, $J=2.5$ Hz, 1H), 5.00 (dd, $J=11.3$; 2.5 Hz, 1H), 4.61 (d, $J=11.3$ Hz, 1H), 4.29–4.08 (m, 2H), 1.02 (t, $J=7.2$ Hz), 0.53 (s, 3H), 0.47 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 169.0, 168.3, 164.8, 137.3, 136.9, 136.5, 131.3, 130.6, 130.5, 128.6, 128.0, 127.9, 127.8, 125.7, 121.7, 120.0, 119.0, 110.9, 109.5, 106.6, 61.1, 58.2, 52.5, 52.3, 44.2, 28.8, 28.6, 13.9; HRMS calcd for $C_{32}H_{29}NO_6$ 523.1994. Found 523.1989.