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Synthesis of carbazoles by a balanced four component condensation

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Abstract—An access to functionalised tetrahydrocarbazoles by a multicomponent reaction including 2-substituted indoles, aromatic aldehydes and Meldrum's acid is described.
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Since its discovery, the combinatorial chemistry has become an integrated part of the modern drug discovery process for both finding and optimisation of lead compounds. However, despite early encouraging results, the preparation of large libraries was unsatisfying, owing to low diversity and lack of rational ligand selection methods. Facing the challenge of generating smaller, more diverse libraries, multicomponent reactions (MCR) have proved to be an effective tool,[1] allowing the easy and rapid preparation of drug-like heterocycle based libraries. Recently Lehn[2] and Sanders and co-workers[3] proposed a dynamic approach in which the target (biomolecule) could organise the connection between the elements of the library, selecting 'tailor made' ligands. For this purpose, the basic components of the library should react with each other reversibly, shifting the library towards the best target fitting ones.

For some years we have been working on the Yonemitsu condensation[4] between indole, Meldrum's acid and various aldehydes.[5] Extending this three-component reaction to 2-substituted indoles **1**,[6] a variety of scaffolds **2**–**6** was prepared depending on the conditions of the reaction (temperature, solvent, catalyst, reagents) (Scheme 1).

The intermediate Knoevenagel adduct **2** was sometimes observed, while the well-known bis-indoles **3** were obtained nearly quantitatively when $Yb(OTf)_3$ was added to the mixture.[7] Dimer **6**, accompanied by a stereoisomer was isolated from the trimolecular mixture in dichloromethane, in the presence of $POCl_3$ (2 equiv).

In this letter we focus our attention on the preparation of the four-component (4-CR) derivatives **5** bearing a Meldrum's acid moiety, suitable for further functional group transformations. One of these structures has already been obtained serendipitously in low quantities (**4**, Ar = Ph) in our previous work.[6]

Initially, we tried to drive our condensation exclusively towards the four-component products **5**. As both malonic and indolyl acetate carbons are able to stabilise a negative charge, various conditions were tried. Finally, we found that on heating a benzene solution of a stoichiometric mixture of ethyl 2-indolyl acetate **1**, Meldrum's acid and benzaldehyde in a Dean–Stark apparatus, the expected carbazole **5a**, accompanied by an inseparable stereoisomer (**5′a**) was isolated in modest yield (43%) (Scheme 2, Table 1).[8] This low yield probably derives from the varying quality of benzaldehyde owing to its Cannizzaro-type disproportionation.

When we used aldehydes such as 2,5-dimethoxybenzaldehyde or 2-nitrobenzaldehyde (entries 2, 3) under the same conditions, compounds **5b** (**5′b**) or **5c** (**5′c**) were isolated[9] in slightly better yields (53–54%). Further improvements in chemical yield, selectivity and purity were achieved by microwave assisted condensation. A strong and short activation gave the highest yield (64%) of the series (entry 4). This tetramolecular condensation was successfully expanded to other 2-substituted indoles and arylaldehydes with different substitution patterns (entries 5–7). Detailed NMR measurements (COSY, HMBC, HMQC, NOE and coupling constants) allowed

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Keywords: Indoles; Multicomponent reaction; Tetrahydrocarbazoles.

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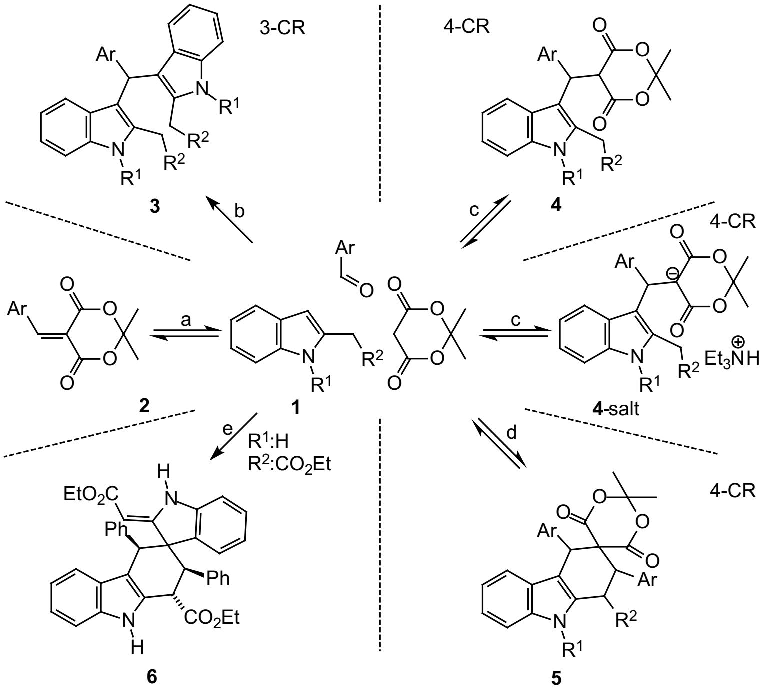
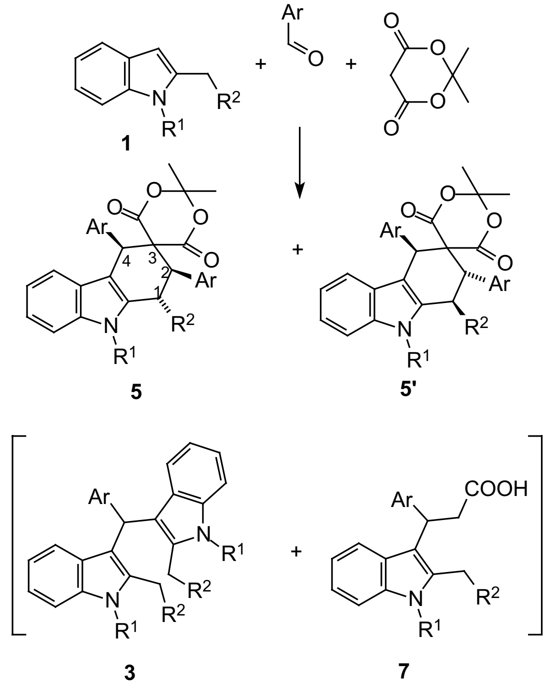


Scheme 1. Reagents and conditions: (a) benzene, reflux, silica gel; (b) Yb(OTf)$_3$; (c) Ref. 6; (d) this work; (e) POCl$_3$ (2 equiv).



Scheme 2.

the complete assignment of the signals of both isomers (**5** + **5′**) as depicted in Scheme 2.

Inevitably, in all cases side products resulting from competing reactions, like di-indole **3** or the substituted indolyl-propionic acid derivatives **7** were also isolated. For the formation of the latter thermal decomposition of the Meldrum's acid moiety of **4** via a ketene intermediate could be proposed.[10]

Mechanistically, the pivotal Knoevenagel adduct **2** could react either with the indoloquinodimethane intermediate **8** or with the 2-vinyl indole **9** in a Diels–Alder reaction,[11] or via a tandem Michael addition–cyclisation (Scheme 3).

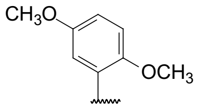
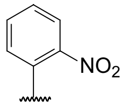
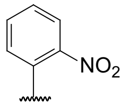
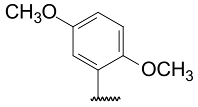
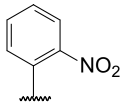
When 1,2-dimethylindole, benzaldehyde and *N*-methylmaleimide were heated under reflux in toluene, the Diels–Alder adduct **10** was obtained in 26% yield (Scheme 4). If toluene was replaced by benzene no reaction occurred even after a 1-day reflux. However, addition of Meldrum's acid and D,L-proline as catalyst to the dienophile-containing mixture gave tetrahydrocarbazoles **5d** and **5′d**.

Other arguments, such as the role of proline as a Michael reaction catalyst,[12] and the reversibility and stereochemistry of the major stereoisomers are all in favour of a stepwise ionic process.

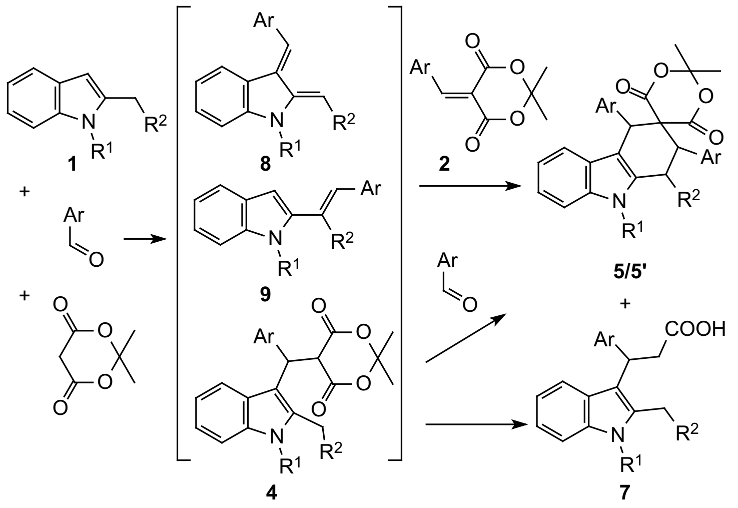
This condensation is not reserved to 2-carbon substituted indoles, as indole-2-thione reacted smoothly with benzaldehyde and Meldrum's acid to give thiacarbazole **11**[13] in 67% yield, as the sole isomer (Scheme 5).

Although the reversibility was a major drawback to higher yields, it is essential for the preparation of tetramolecular condensation-guided dynamic libraries. For these purposes, we carried out two sets of experiments, the first starting from a trimolecular adduct **4** (Scheme 1), the second using two different aldehydes in a tetramolecular condensation.

Table 1. Tetramolecular condensations between 2-substituted indoles, Meldrum's acid and arylaldehydes

Entry		R^1	R^2	Ar	Method	**5** + **5′**[a] (%)	**3** (%)	**7**[b] (%)
1	**a**	H	CO_2Et	Ph	A	43 (95/5)	15	18
2	**b**	H	CO_2Et		A	53 (86/14)	8	—
3	**c**	H	CO_2Et		A	54 (70/30)	—	[c]
4	**c**	H	CO_2Et		B	64 (93/7)	—	13
5	**d**	CH_3	H	Ph	A	53 (87/13)	7	[c]
6	**e**	CH_3	H		A	41 (95/5)	14	—
7	**f**	CH_3	H		A	26 (84/16)	21	[c]

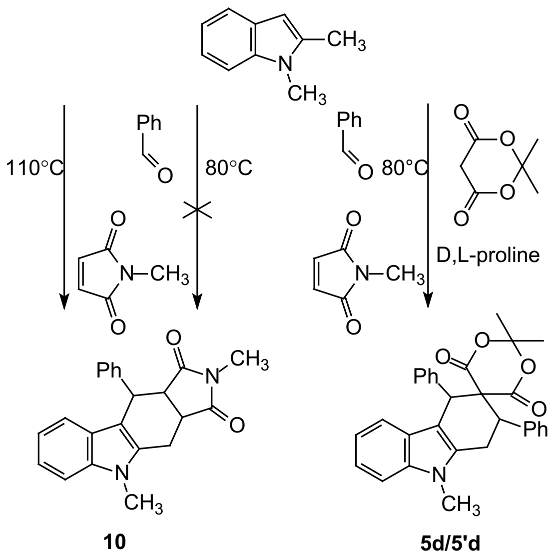
[a] Diastereomeric ratios were determined by ^1H NMR.
[b] Determined after methylation by CH_2N_2.
[c] Detected by ^1H NMR but not isolated.



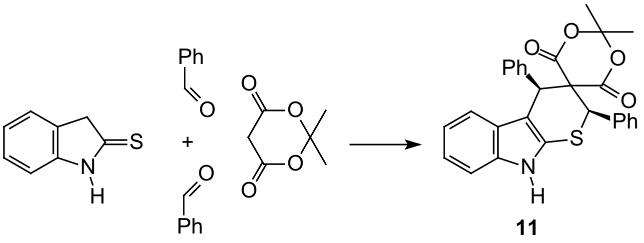
Scheme 3.

In both cases, *p*-fluorobenzaldehyde was chosen as the 'second' aldehyde in order to facilitate the study of the reaction mixture on the basis of ^{19}F NMR and low resolution mass spectrometry.

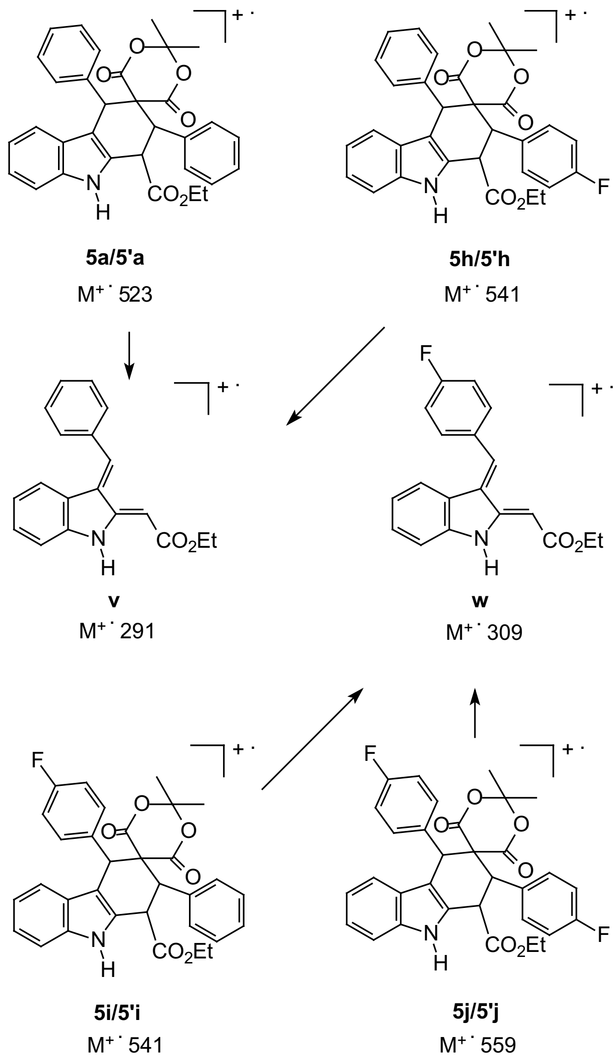
In the first experiment the triethylammonium salt **4a** was heated at 70 °C with *p*-fluorobenzaldehyde in acetonitrile for 1 day. Although 22% of **4a** decomposed by thermolysis to the acid **7**, a mixture of inseparable nonfluorinated carbazoles **5a**/**5′a** and fluorinated ones **5h**/**5′h** was isolated in about 20% yield. The presence of a nonfluorinated phenyl substituent attached at the C-2 position of the carbazole ring proved that the starting trimolecular adduct **4a** had reversed to its starting materials, especially to benzaldehyde, which was also incorporated into the carbazole ring system. Apart from



Scheme 4.



Scheme 5.



Scheme 6.

the signals C$_{\text{arom}}$–F at about $\delta = 161$ ppm, neither ^{1}H, nor ^{13}C NMR spectra allowed the determination of the composition of this inseparable mixture. However, the location of the *p*-fluorophenyl group at C-2 in **5h/5′h** (and not at C-4) was ascertained by mass spectrometry studies. The retro-diene fragment **v** *m*/*z* 291, including the 'southern' position (C-2) is derived from both molecular ions $C_{32}H_{29}NO_6$ (*m*/*z* 523) and $C_{32}H_{28}NO_6F$ (*m*/*z* 541).

In the second set of experiments, the two aldehydes (benzaldehyde and *p*-fluorobenzaldehyde) were mixed in equimolar quantity with Meldrum's acid and ethyl 2-indolyl acetate in acetonitrile in the presence of 0.1 equivalents of D,L-proline. After 4 days, an inseparable mixture of four carbazoles **5a/5′a**, **5h/5′h**, **5i/5′i**, **5j/5′j** was obtained by column chromatography (27%).

The presence of peaks *m*/*z* 523, and *m*/*z* 559 in the mass spectrum of the isolated mixture supported the presence of the two homogenous derivatives **5a** and **5j**. As for the mixed structures, a study of the above mentioned fragmentations unambiguously confirmed that both regioisomers **5h** and **5i** were formed in the reaction. Ion **v** (*m*/*z* 291) originates from **5a** and **5h**, whereas fragment **w** (*m*/*z* 309) results from **5i** and **5j**. Metastable ion decomposition studies of the molecular ions by linked-scan methods unambiguously showed that ion **v** is a common daughter of two fathers **5a/5′a** and **5h/5′h**, as well as **w** is that of **5i/5′i** and **5j/5′j** (Scheme 6).

To summarise, we have found a multicomponent condensation of various aldehydes with 2-substituted indoles and Meldrum's acid for the preparation of functionalised 1,2,3,4-tetrahydrocarbazoles. As these reactions appear to be reversible, they could be a first step towards the development of a combinatorial version of the Yonemitsu reaction.

Acknowledgements

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8. General procedure for the preparation of compounds **5a**–**g** *Method A*: To a stirred solution of 2-substituted indoles (2 mmol) in benzene (15 mL), Meldrum's acid (2 mmol), the arylaldehydes (4 mmol) and D,L-proline (0.2 mmol) were added successively. The mixture was warmed at 80 °C for 3 of 11 h. *Method B*: To a solution of the 2-substituted indoles (1.5 mmoles) in dry benzene (3 mL), molecular sieves (4 Å), D,L-proline (0.1 mmol), Meldrum's acid (1.5 mmol) and the arylaldehydes (3 mmol) were added successively. The mixture was heated under a Dean–Stark trap by microwave irradiation: 250 W (5 min at 85 °C, CEM Discover® apparatus). After evaporation of the solvent under reduced pressure the residue was purified by chromatography on silica gel (CH_2Cl_2/cyclohexane 10%, or CH_2Cl_2/MeOH 0–6%) to give a mixture of diastereomers **5** and **5′**.
9. All new compounds gave satisfactory spectral data. For example, selected data for major isomer **5c**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.50 (s, 1H), 7.90–7.79 (m, 3H), 7.67 (d, $J = 7.9$ Hz, 1H), 7.51 (t, $J = 7.4$ Hz, 2H), 7.42–7.24 (m, 4H), 7.16 (t, $J = 7.1$ Hz, 1H), 6.99 (t, $J = 7.1$ Hz, 1H), 6.05 (s, 1H), 5.50 (d, $J = 10.9$ Hz, 1H), 5.06 (d, $J = 10.9$ Hz, 1H), 4.20 (q, $J = 7.2$ Hz, 2H), 1.70 (s, 3H), 1.17 (t, $J = 7.2$ Hz, 3H), 0.97 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.9, 166.7, 165.8, 151.5, 149.4, 136.7, 136.6, 132.2, 130.9, 129.3, 129.0, 125.7, 125.6, 125.1, 122.9, 120.1, 118.5, 111.2, 107.9, 106.5, 62.1, 60.5, 46.5, 42.3, 35.6, 30.4, 26.1, 13.7; HREIMS calcd for $C_{32}H_{27}N_3O_{10}$: 613.1696, found: 613.1695; Anal. calcd for $C_{32}H_{27}N_3O_{10}$: C, 62.64; H, 4.43; N, 6.85. Found C, 62.67; H, 4.06; N, 6.77.
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13. Selected data for **11**: mp 157–158 °C; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 10.20 (s, 1H), 7.60–6.88 (m, 12H), 6.64 (t, $J = 7.7$ Hz, 1H), 5.96 (d, $J = 7.7$ Hz, 1H), 5.40 (s, 1H), 5.20 (s, 1H), 0.70 (s, 3H), 0.46 (s, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 167.5, 167.3, 137.3, 136.1, 134.4, 133.0, 130.9, 130.2, 129.9, 129.3, 129.0, 128.9, 128.7, 128.6, 128.5, 128.4, 126.6, 120.4, 118.5, 118.1, 110.6, 105.8, 105.7, 59.5, 52.9, 49.0, 29.7, 28.1; MS (FAB+) 470 $[M+H]^+$ (37), 238 (100).