Indole based multicomponent reactions towards functionalized heterocycles

Janos Sapi* **and Jean-Yves Laronze**

UMR CNRS 6013 "Isolement, Structure, Transformations et Synthèse de Substances Naturelles", IFR 53 "Biomolécules", Faculté de Pharmacie, Université de Reims-Champagne-Ardenne, 51 rue Cognacq-Jay, F-51096 Reims Cedex, France

E-mail: janos.sapi@univ-reims.fr

Dedicated to Professor Dr. Sándor Antus on the occasion of his 60th birthday

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Abstract

This short review offers a non-exhaustive panorama of the indole ring implicated multicomponent reactions, and simple functional group transformation-based approaches, developed over the last thirty years for the synthesis of various biologically interesting indole heterocyclic ring systems.

Keywords: Multicomponent reactions, indole derivatives, alkaloids, nitrogen heterocycles, Mannich reaction, gramines, Ugi reaction, Petasis reaction, domino reactions, Yonemitsu reaction, trimolecular condensation, Meldrum's acid, Curtius rearrangement, β-substituted tryptophan, tryptamine derivatives, β-carboline, spiro-oxindole derivatives, tetrahydro carbazole derivatives

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Introduction

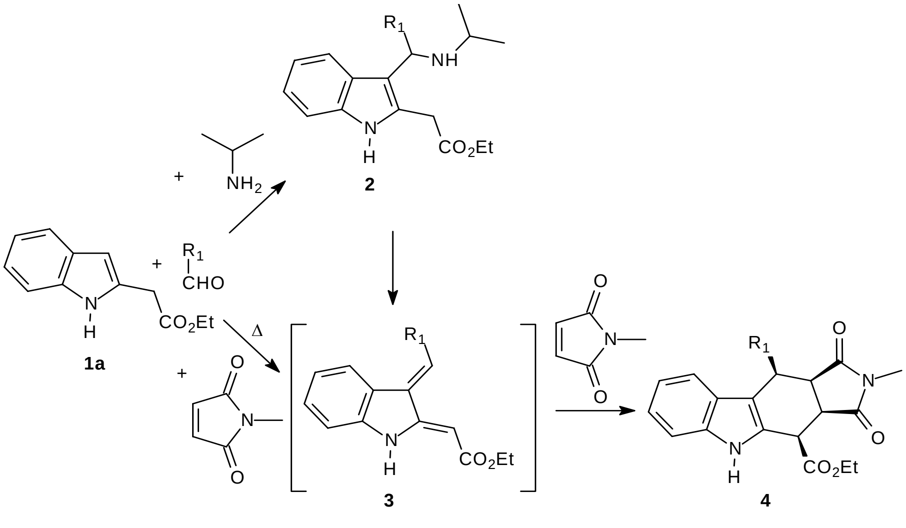
Multicomponent reactions (MCR-s) have recently emerged as valuable tools in the preparation of structurally diverse chemical libraries of drug-like heterocyclic compounds.[1] The multicomponent reaction story began as far back as 1850 by the publication of the Strecker reaction,[2] arriving nowadays at its apogee. During this one and a half century period, some notable achievements include the discovery of the Biginelli,[3] the Mannich,[4] and the Passerini[5] reactions culminating in 1959 when Ugi published[6] probably the most versatile MCR based on the reactivity of isocyanides.[7] In view of the increasing interest for the preparation of large heterocyclic compound libraries, the development of new and synthetically valuable multicomponent reactions remains a challenge for both academic and industrial research teams.[8]

Although functionalized indole ring systems have been found frequently in biologically active molecules, indole derivatives as MCR partners are rather under-represented. This review offers a short and non-exhaustive summary of the synthesis of functionalized heterocyclic systems by multicomponent strategies involving indole derivatives as reaction partners.

1. Mannich reaction-“Gramine chemistry”

The condensation of activated carbonyl compounds with *in-situ* formed iminium species, called the Mannich reaction, provides β-amino carbonyl compounds.[4] When such iminium species undergo nucleophilic attack by indole derivatives, gramines can be prepared.[9] From a preparative point of view the generally unstable gramines are very important intermediates towards various tryptamine, tryptophan, β-carboline,[9,10] carbazole[11] and other indole alkaloids.[12] Additionally, some gramine derivatives have been found to be potent 5-HT$_6$ receptor ligands.[13]

Recently, Lévy *et al.* have successfully exploited the thermal instability of 2-substituted gramines **2** for the *in-situ* generation of indole-2,3-quinodimethanes **3** which were engaged as reactive dienes in Diels-Alder reactions to afford 1,2,3,4-tetrahydrocarbazoles (Scheme 1).[14]

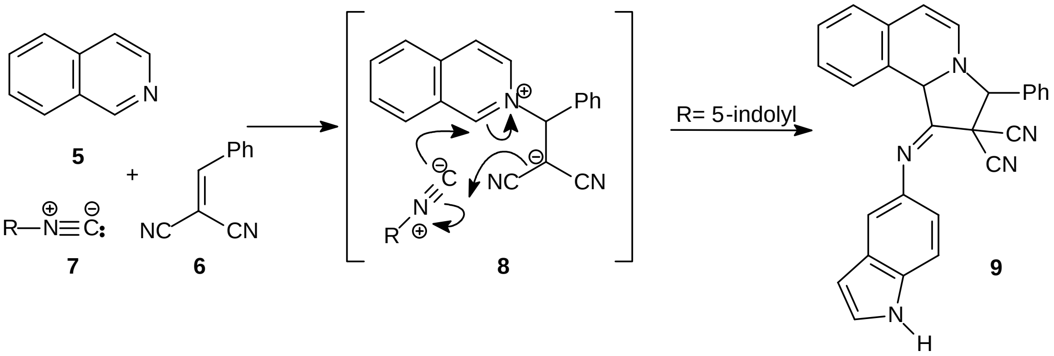


Scheme 1

In this process, in the absence of an amine component, a simple multicomponent approach employing an equimolar mixture of ethyl 2-indolylacetate **1a**, benzaldehyde and *N*-methylmaleimide resulted in the formation of **4** in 74% yield.

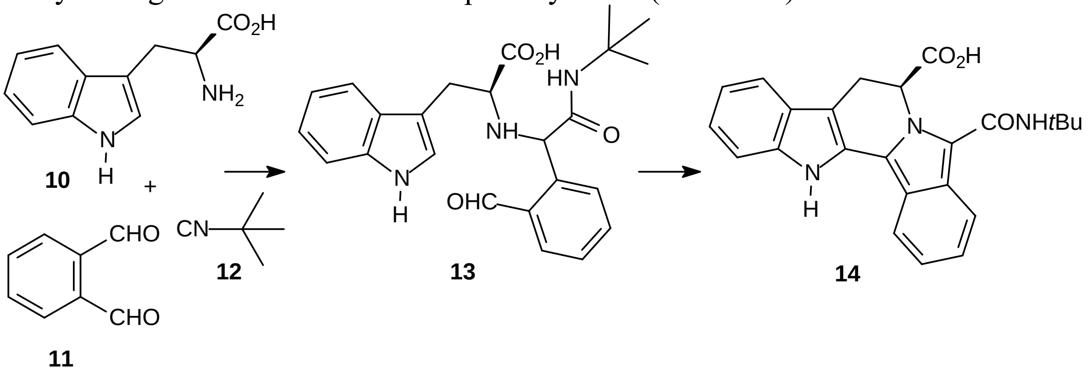
2. MCR-s involving isocyanides-Ugi reaction

Despite the importance of Ugi-type reactions in the synthesis of heterocyclic compounds, only scant attention has been paid to the incorporation of indoles as multicomponent reaction partners. For example, the indole nucleus has a secondary role in a recently published preparation of pyrrolo[2,1-*a*]isoquinoline derivatives. Mironov *et al*. have found a new MCR between isoquinoline **5**, geminal diactivated olefins **6**, and isocyanides **7**, for the synthesis of dihydro-10*H*-pyrrolo[2,1-*a*]isoquinolines (Scheme 2).[15] From a mechanistic point of view, the key step is the formation of zwitterion **8**, which was attacked by isocyanide affording the final product **9**.



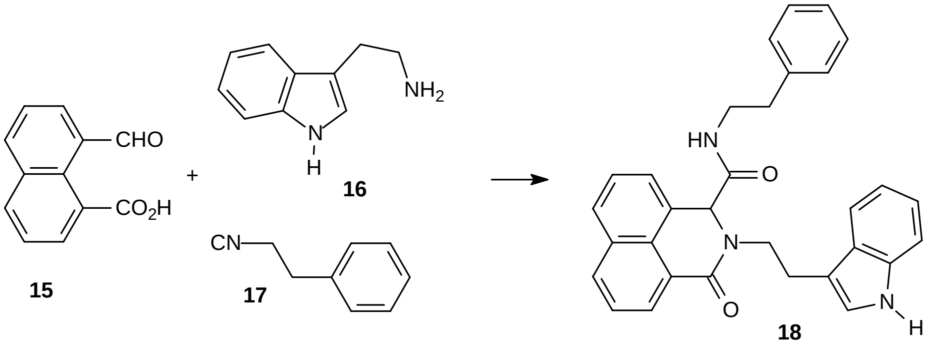
Scheme 2

The β-carboline core is a frequently occurring structural motif in natural products and biologically active substances. For the preparation of a pentacyclic β-carboline structure Dömling *et al*. proposed an Ugi-type reaction condensing tryptophan **10** with phthalic dialdehyde **11** and isocyanide **12**. Spontaneous Pictet-Spengler cyclization of the Ugi-intermediate **13**, followed by D-ring oxidation afforded the pentacycle **14** (Scheme 3).[7a]



Scheme 3

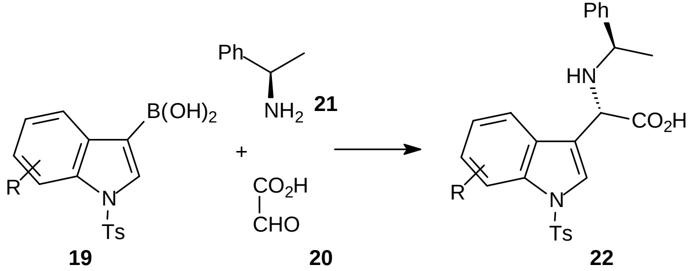
A modified version of the Ugi four component reaction, using bifunctional aldehyde acid **15**, tryptamine **16**, and isocyanide **17** as starting materials, has been worked out by Zhang *et al.* for the synthesis of various, including indole containing, polycyclic lactams **18** (Scheme 4).[16]



Scheme 4

3. MCR-s with boronic acids-Petasis reaction

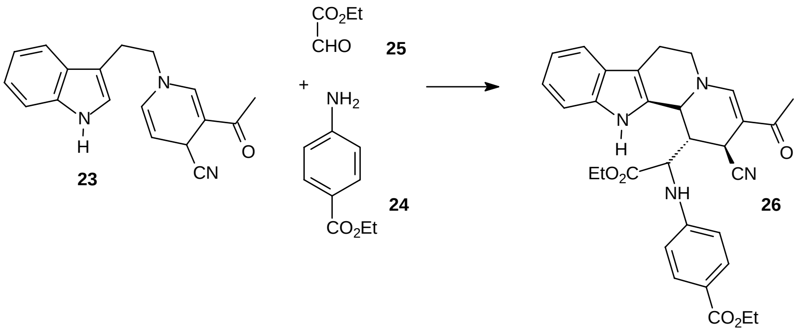
In the '90-s, a new synthetic method, involving vinyl boronic acids as nucleophiles in Mannich type reactions was developed by Petasis for the preparation of various allylamines.[17] Later on, this approach was extended to the preparation of non-natural amino acids. Thus, a trimolecular condensation involving diverse 3-indolyl boronic acids **19**, glyoxalic acid **20**, and a chiral amine **21** allowed the preparation of *N*-substituted-indolylglycines **22** (Scheme 5) with excellent diastereoselectivity (de>99%).[18]



Scheme 5

4. Multicomponent reactions using dihydropyridines

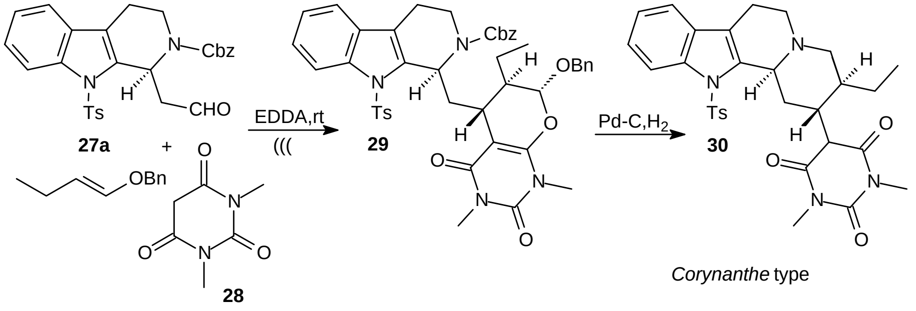
For a long time, calcium channel antagonist dihydropyridines have been attractive targets for multicomponent approaches (Hantzsch reaction,[19] 1882). The high diversity, the ready access and the reactivity of the enamine appendage make them versatile intermediates for further synthetic transformations. Thus, Lavilla *et al.* have developed recently a dihydropyridine-based multicomponent approach for the preparation of new pyridine annulated tetrahydroquinoline derivatives through a lanthanide catalyzed formal [4+2] cycloaddition. When *N*-tryptophyl dihydropyridine **23** was reacted with anilines **24** and ethyl glyoxalate **25** under $InCl_3$ mediated catalysis, the indoloquinolizidine derivative **26** was isolated as a 4:1 mixture of epimers on the aminoester moiety (Scheme 6). The observed diastereoselectivity was rationalized by a preferential attack of the dihydropyridine from the less hindered face of the imine, whereupon final cyclisation of indole onto the intermediate iminium species takes place with total stereocontrol leading to *trans*-indoloquinolizines.[20]



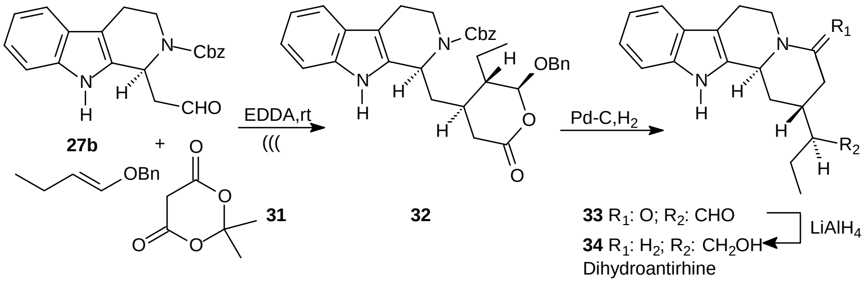
Scheme 6

5. Multicomponent reactions combined with domino cyclisation

Domino reactions[21] involving the formation of several chemical bonds in one sequence without isolating the intermediates, have proven to be economically and environmentally favourable procedures for the preparation of complex molecules. A successful combination of domino reactions with the multicomponent approach tends towards the ideal organic synthesis concept. Following this idea, a three component condensation domino Knoevenagel-hetero Diels-Alder pathway was worked out by Tietze *et al*. for the preparation of indole alkaloid derivatives (**30** and **34**, respectively) of the *Corynanthe* (Scheme 7) and *Valesiachotamine* (Scheme 8) groups.[22] In both reactions, high diastereoselectivity was observed and the configuration of the newly formed stereogenic centres can be reversed by changing the tosyl group (**27a**) at the indole nitrogen into hydrogen (**27b**) or vice-versa.[23]

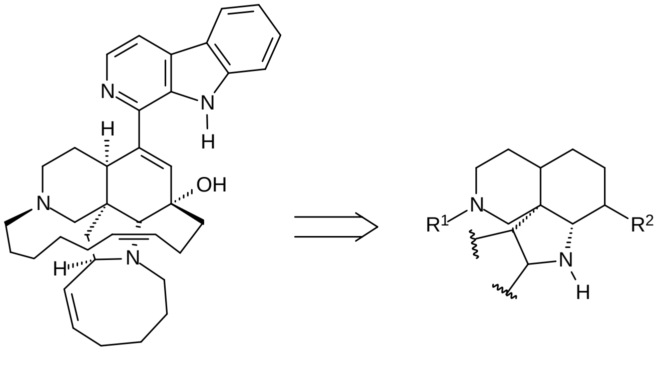


Scheme 7



Scheme 8

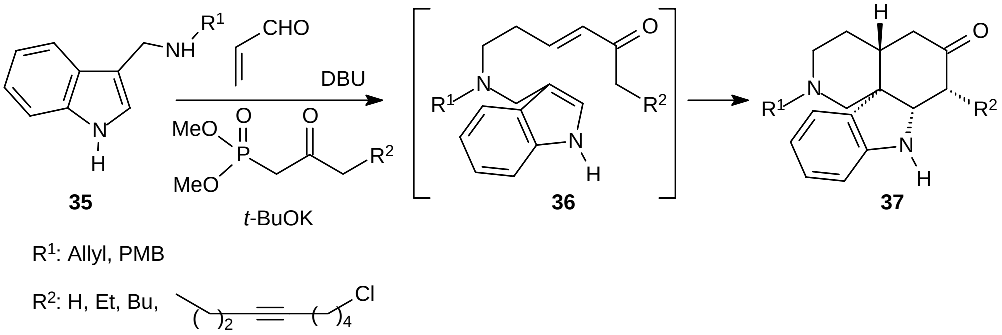
With an aim towards constructing the central isoquinoline based tricyclic core of the anticancer alkaloids manzamine (Scheme 9), Markó *et al*. have proposed a novel cascade anionic polycyclisation method.[24]



manzamine A

Scheme 9

Their procedure is situated somewhere on the borderline between multicomponent and domino reactions. Substituted gramines **35**, in the presence of *t*-BuOK reacted with acrolein and functionalized β-keto phosphonates via a multicomponent condensation, followed by base catalyzed polycyclisation cascade of **36** to afford highly substituted decahydro-isoquinoline type compounds **37** (Scheme 10). This highly chemo- and diastereoselective process allowed the control of up to four chiral centres.

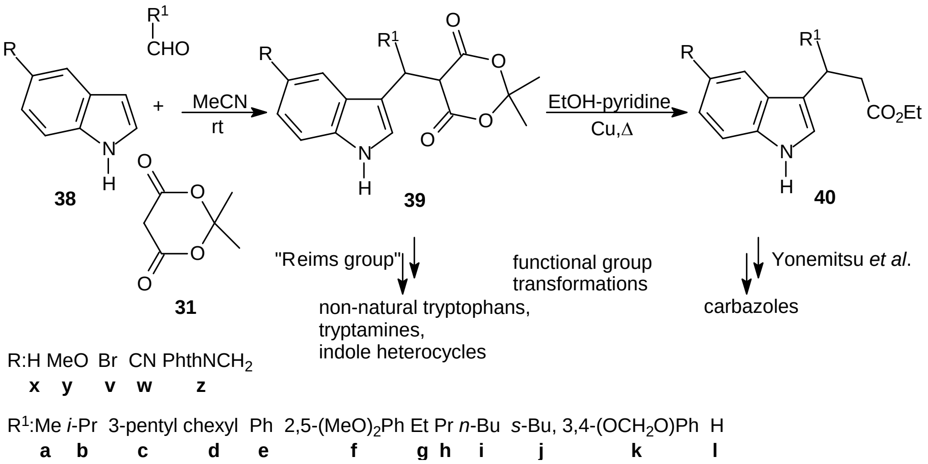


Scheme 10

6. Yonemitsu-reaction

Meldrum's acid **31** appears to be an attractive reagent in organic syntheses owing to its high acidity, steric rigidity and high reactivity.[25]

In 1978, Yonemitsu *et al*. found a new multicomponent reaction (Scheme 11) by reacting indole **38**, Meldrum's acid **31** with different aldehydes.[26] Subsequent decarboxylative ethanolysis of adducts **39** led to various ethyl 3-substituted indolyl-propionates **40**, used as intermediates in the synthesis of complex indole alkaloids.[27]



Scheme 11

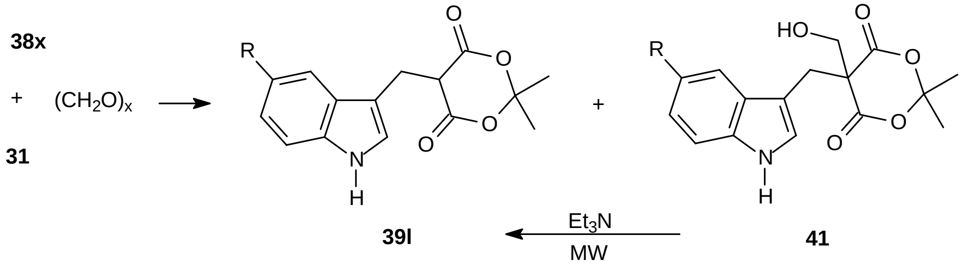
6.1. Synthesis of β-substituted tryptophans

Tryptophan is an important essential amino acid present in various biologically active peptides. Its replacement by conformationally constrained β-substituted analogs has been used commonly in peptide-receptor affinity studies.

When, at beginning of the ’90-s, we were interested in the preparation of non-natural β-substituted tryptophan derivatives for the synthesis of modified CCK-4 analogs[28], the Yonemitsu reaction attracted our attention. Stable, high-yield isolated products with the readily cleavable dioxanedione appendage seemed to be valuable intermediates for our purposes.

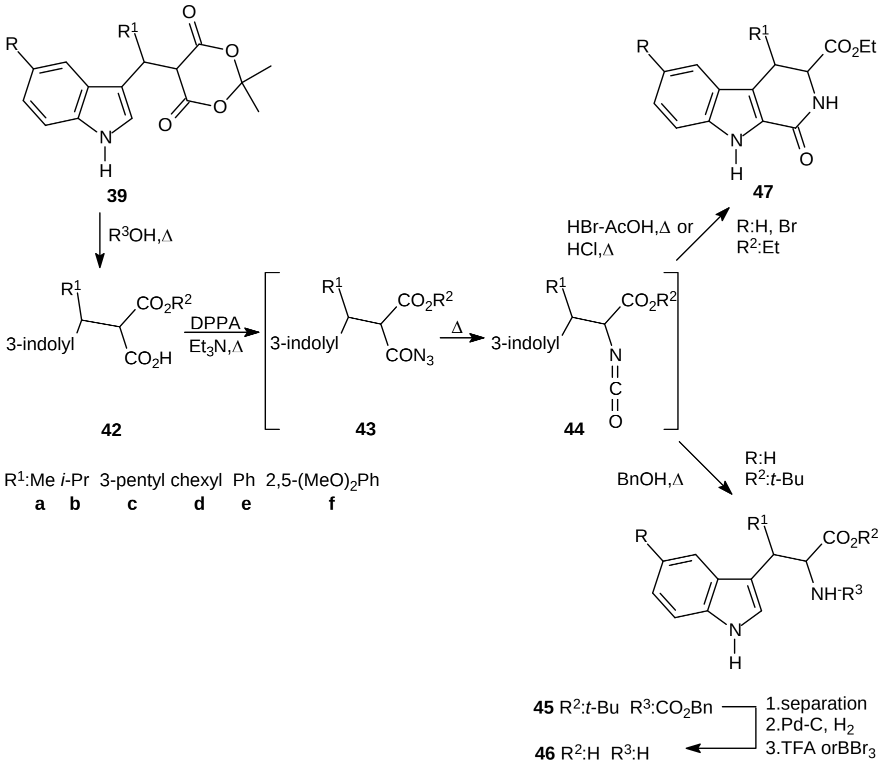
Consistent with Yonemitsu’s report[26], indoles **38** with various alkyl-, or arylaldehydes and Meldrum’s acid **31** smoothly gave the condensation products **39** (Scheme 11) (75-95 %).[29]

Condensation with paraformaldehyde led to a mixture of normal adduct **39l** and its hydroxymethyl counterpart **41** which could be quantitatively converted into **39l** under microwave irradiation (Scheme 12).[30]



Scheme 12

Solvolysis of **39** with alcohols gave a diastereomeric mixture of acid esters **42** (Scheme 13). For the transformation of the carboxylic acid function into carbamate, the well-known domino acylazide **43** formation-Curtius rearrangement-benzylalcohol mediated solvolysis of the isocyanate intermediate **44** procedure was utilized. Separation of the diastereomeric carbamates **45** (*syn*/*anti*), followed by classical deprotection completed the synthesis of β-substituted tryptophans **46** (*syn*/*anti*).[31]



Scheme 13

When the Curtius rearrangement was carried out in an acid medium, 4-substituted 1-oxo-tetrahydro-β-carboline derivatives **47** were isolated in 40-68 % overall yield (Scheme 13.).[32] The 1-Oxo-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid ester **47** (R:H**)** core is considered as a rigid pseudopeptide analog of tryptophan and could represent a valuable scaffold for the synthesis of futher functionalized polycyclic systems of biological interest.

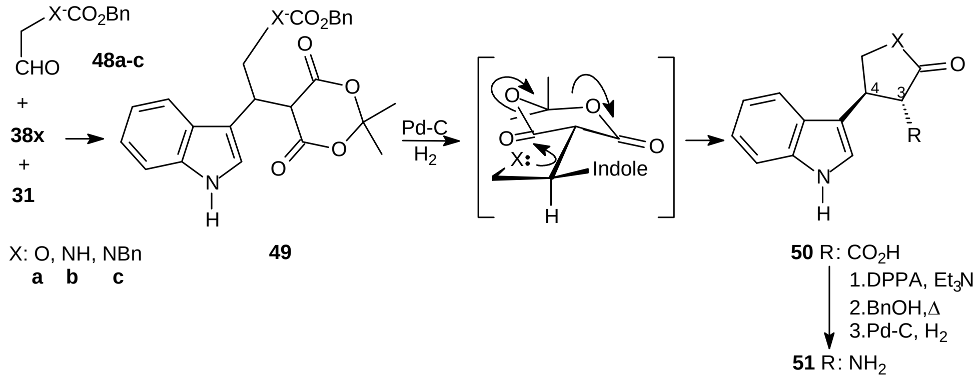
6.2. Synthesis of heterocycle-fused tryptamines

The tetrahydro-β-carboline core, present in numerous alkaloids (*Vinca*-, *Rauwolfia*-, *Harman*-alkaloids) and synthetic products with valuable biological properties, is accessible from tryptamine *via* the well-known Pictet-Spengler[33] and Bischler-Napieralski reactions. Some 3,4-annulated (tetrahydro)-β-carbolines were reported to be potent benzodiazepine antagonists or tyrosine kinase inhibitors.[34] Heterocycle fused tryptamines are considered as useful precursors for the preparation of functionalized, conformationally restricted serotonin and melatonin analogs.

A multicomponent pathway, using masked nucleophile containing aldehydes, was proposed for the preparation of new 3,4-heterocycle fused (tetrahydro)-β-carbolines. Following a chemoselective deprotection, an internal nucleophilic ring opening of the Meldrum's acid moiety could be envisaged and the resulting carboxylic acid function was to be relayed toward the targeted tryptamine and β-carboline compounds.

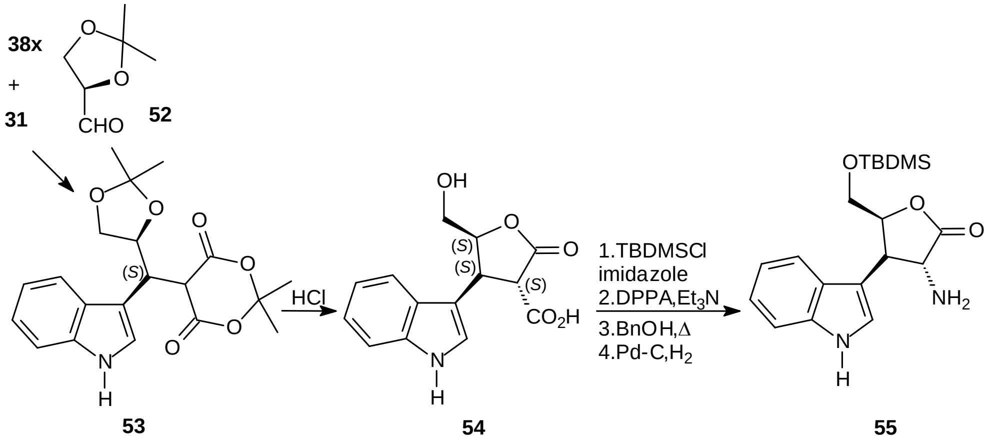
In a preliminary study,[35] the trimolecular adducts **49** were prepared by using Cbz (CO_2Bn) masked 2-hydroxy- **48a** or 2-aminoacetaldehydes **48b,c** as aldehyde partners (Scheme 14). Deprotection of **49** and subsequent internal nucleophilic attack allowed the isolation of furanone

50a (90 %), and pyrrolidinone **50b** (80 %), as sole products. In both cases, we observed the exclusive formation of 3,4-*trans* disubstituted ring systems, resulting from a decongested transition state in which the bulky indole ring, being remote from the Meldrum's acid moiety, favours an equatorial attack. Conversion of the carboxylic acid function to amine followed the classical pathway providing heterocycle-fused *trans* tryptamines **51a** or **51b**.



Scheme 14

It was then interesting to investigate whether a chiral aldehyde, possessing the same type of masked nucleophile, could control the trimolecular condensation step. For this purpose, 2,3-*O*-isopropylidene-D-glyceraldehyde (-)-**52**, as a chiral template, was reacted with indole **38x** and Meldrum's acid **31** affording condensation product (-)-**53** as the sole diastereomer (Scheme 15) (75 %).



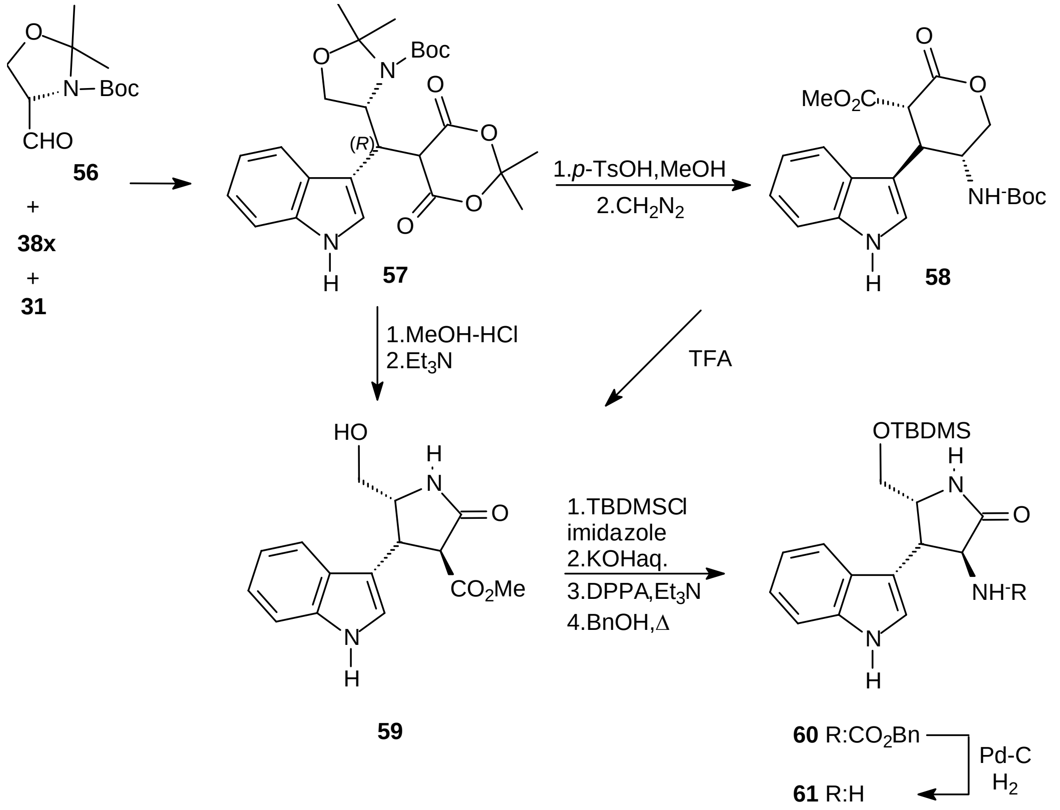
Scheme 15

As expected, a subsequent deprotection-spontaneous cyclization sequence gave the corresponding lactone acid (-)-**54**, enabling the complete diastereocontrol of the two newly created stereocenters.[36] Transformation of (-)-**54** into furan fused chiral tryptamine (+)-**55** was performed by the classical manner.

Continuing our program, we sought to investigate the chemoselectivity of the internal ring opening of the Meldrum's acid unit by using Garner's aldehyde[37] **56**, an orthogonally protected bifunctional chiral aldehyde. In the event, trimolecular condensation of Garner's aldehyde **56** with indole **38x**, and Meldrum's acid **31** provided the corresponding adduct (-)-**57** (90 %) in high (de >90%) diasteroselectivity (Scheme 16).

Depending on the reaction conditions, chemoselective internal *O*- or *N*-nucleophilic ring closures were observed. Careful isopropylidene deprotection of (-)-**57** followed by esterification allowed the isolation of diastereomerically pure pyranone-fused tryptamine derivative (-)-**58**.

Deprotection of (-)-**57** in refluxing methanol-HCl provided diastereomerically pure lactam ester (-)-**59**, as a result of a full deprotection, selective internal *N*-nucleophile ring closure sequence, followed by esterification of the carboxylic acid moiety (Scheme 16).

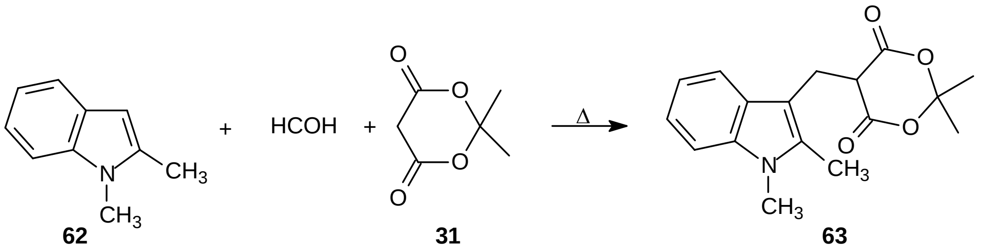


Scheme 16

Simple functional group transformations completed the synthesis of chiral pyrrolidinone-fused tryptamine (-)-**61**.[38] In both series, the chirality of the Garner's aldehyde ensured a complete and predictible control of the two newly created stereocentres.

6.3. Preparation of spiro[pyrrolidinone-indolines]

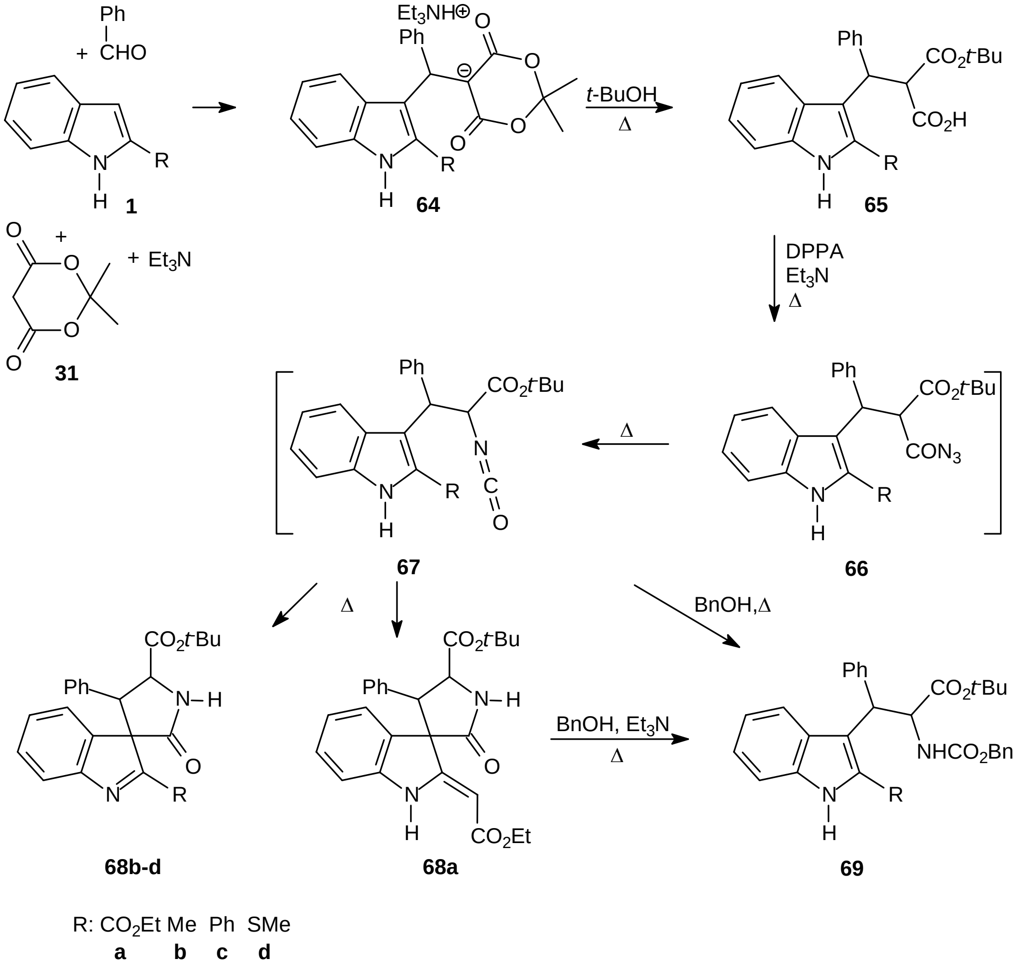
In 1983 Bailey *et al.* successfully applied the Yonemitsu reaction to 2-substituted indoles (Scheme 17). They found that 1,2-dimethylindole **62** reacted with aldehydes and Meldrum's acid **31** giving rise to the expected trimolecular products **63**.[39]



62 **31** **63**

Scheme 17

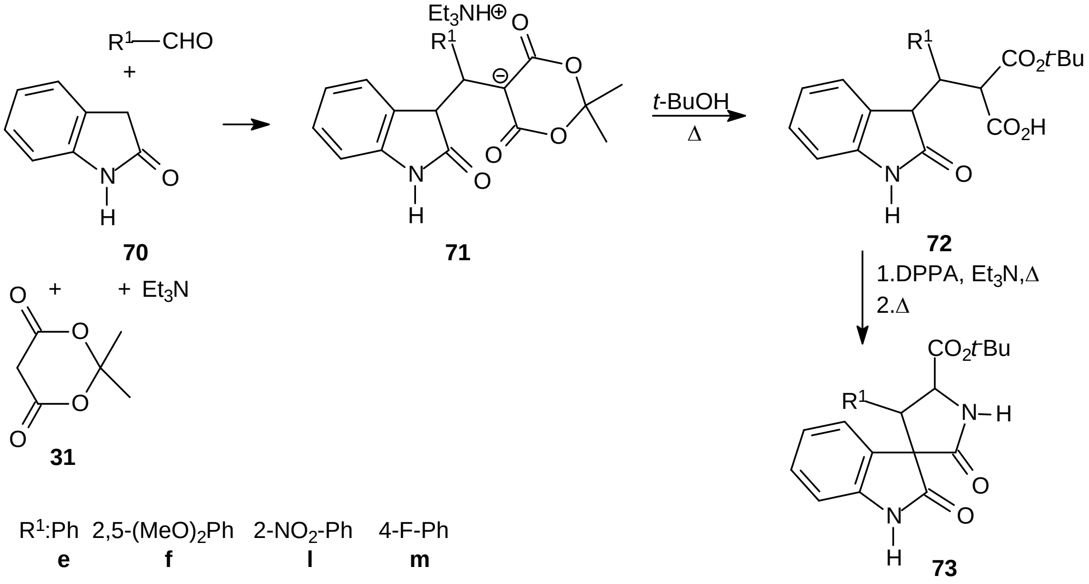
Although our initial investigations to reproduce Bailey's results failed, multicomponent reactions between 2-substituted indoles **1**, benzaldehyde and Meldrum's acid **31** were carried out in the presence of one equivalent of triethylamine affording stable, crystalline adduct salts **64** in 60-78 % yield.[40] It is noteworthy that **64** are obtained *stricto sensu* in tetramolecular reaction processes (Scheme 18).



Scheme 18

When *in situ* formed azides **66**, prepared *via* the well-known path from **65**, were heated in toluene, a diastereomeric mixture of spirocyclic pyrrolidinone-indolines **68** was isolated *via* **67** resulting from a Curtius rearrangement, followed by a thermal spirocyclisation process.

Indoline-2-one (oxindole) **70** also proved to be a reactive nucleophile under modified Yonemitsu conditions. Condensation of **70** with aromatic aldehydes, Meldrum's acid **31** and triethylamine afforded adduct salts **71** in moderate yields. A successful application of the previous domino process on **72** allowed the isolation of functionalized spiro-oxindole derivatives **73**.[41] It is important to note that the spiro-oxindole core is present in various alkaloids, for example horsfiline or spirotyprostatines, of biological interest.

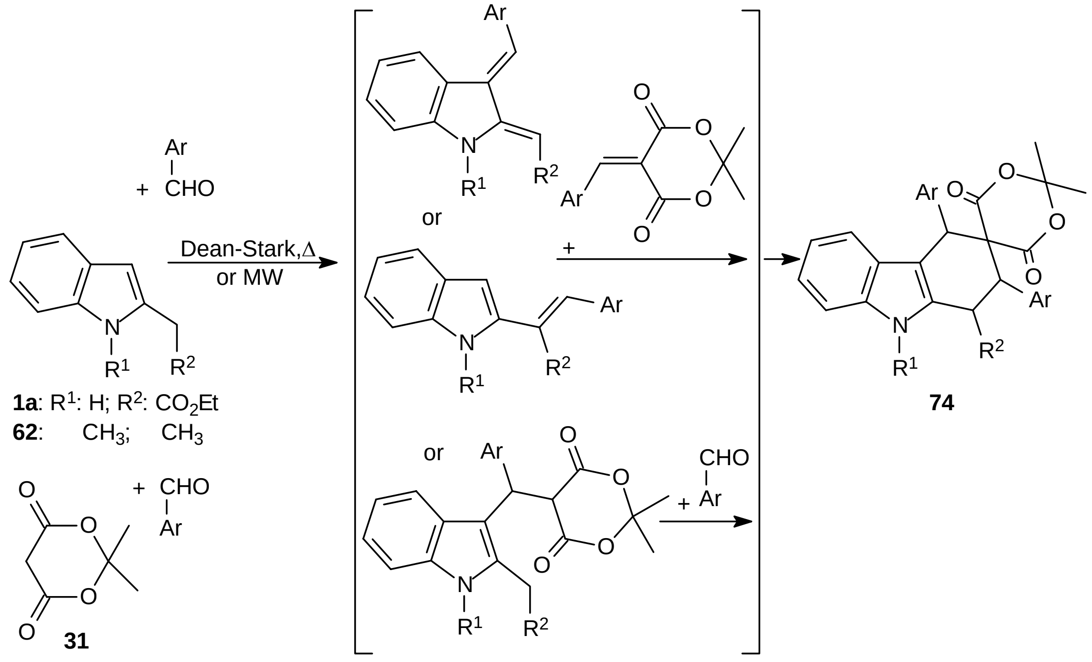


Scheme 19

6.4. Tetramolecular version of the Yonemitsu reaction

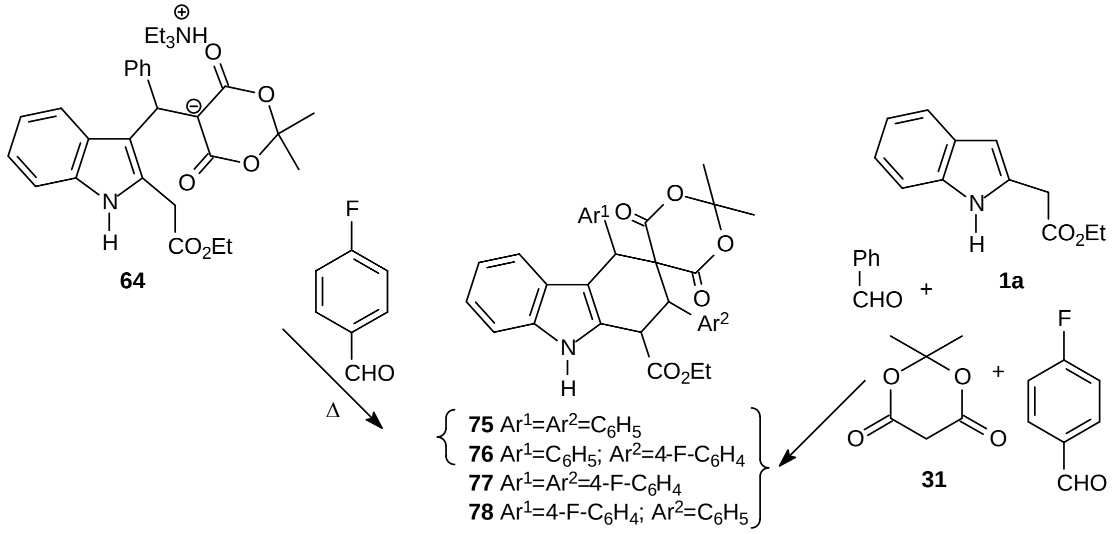
When a mixture of ethyl 2-indolylacetate **1a**, Meldrum's acid **31** and two equivalents of benzaldehyde were heated in a Dean-Stark trap or with a microwave apparatus, functionalized tetrahydrocarbazole derivatives **74** were obtained (Scheme 20). This four-component reaction was expanded to other substituted indoles and arylaldehydes with different substitution patterns. Mechanistically, the pivotal Knoevenagel adduct could react with different *in situ* formed intermediates affording the tetramolecular compounds **74**.

Toward combinatorial utilisation, the reversibility of this process was also studied by using benzaldehyde and 4-fluorobenzaldehyde combined with mass spectral analytical methods. Treatment of salt **64** (R: CH_2CO_2Et) with 4-fluorobenzaldehyde led to a mixture of nonfluorinated **75** and monofluorinated **76** carbazoles, while the reaction of **1a** with **31**, benzaldehyde and 4-fluorobenzaldehyde gave a mixture of all possible tetrahydrocarbazoles **75-78** (Scheme 21). This reaction seems to be the first step towards the development of a combinatorial version of the Yonemitsu reaction.



Ar: C_6H_5; 2,5-$(MeO)_2C_6H_3$; 2-NO_2-C_6H_4

Scheme 20



Scheme 21

7. Conclusions

This short review describes the main synthetic methods that have been published in the field of indole based multicomponent reactions during the last three decades. In spite of some recent progress, particularly concerning the Yonemitsu reaction, multicomponent methodology with the indole ring system as a reaction partner remains to be further explored for the construction of various biologically important heterocyclic compounds.

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