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A REVIEW ON THE SYNTHESIS OF HEXACYCLIC DERIVATIVES USING CONVENTIONAL AND NON-CONVETIONAL METHODS

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ABSTRACT
For several years, there has been increasing interest in developing new hexacyclic derivatives in the field of organic chemistry. The aim of this research was to carry out a review on the synthesis of some hexacyclic derivatives. It is important to mention that reaction protocols imply conventional and non-conventional methods, in particular the use of different solvents and microwave irradiation conditions. Notably, decision-making in the development of new hexacyclic derivatives can rely on protocol reactions.

KEYWORDS. Hexacyclic, synthesis, derivative, microwave

INTRODUCTION
There are several reports in the literature on the synthesis of some heterocyclic[i-v] such as hexacyclic derivatives using different methods.[vii-x] For example, the synthesis of (9S)-9-Ethyl-2,3-dihydro-9-hydroxy-12H-1,4-oxazino-[3,2-f]pyrano[3′,4′:6,7]indolizino[1,2-b]qui-noline-10,13-(9H, 15H)-dione (**1**) from 9-amino-10-(2-bromoethoxy)-(20S)-camptothecin (**2**) and sodium iodide (Figure 1).[xi]

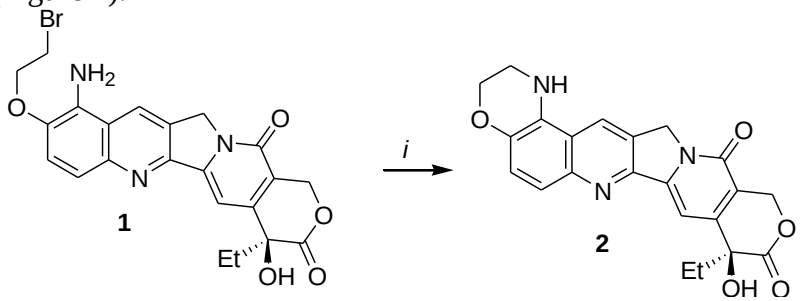

Figure 1. Synthesis of a hexacyclic derivative (1). *Conditions and Reagents*: *i* = K_2CO_3, NaI, acetone, reflux/N_2, 16 h.

Another study (Figure 2) showed the reaction of *N*-(5-amino-4-oxo-thiochroman-8-yl)acetamide (**3**) with (4*S*)-4-ethyl-4-hydroxy-7,8-dihydro-1*H*-pyrano[3,4-f]indolizine-3,6,10-trione (**4**) to form the compound (RS)-4-Amino-1,2-dihydro-9-ethyl-9-hydroxy-12H-thiino-[4,3,2-de]pyrano [3′,4′:6,7]indolizino[1,2-b]quinoline-10,13-(9H,15H)-dione (**5**).[xii]

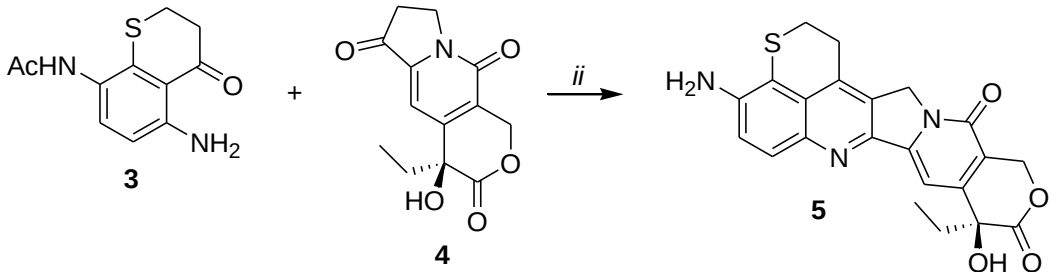

Figure 2. Synthesis of a hexacyclic analog (**5**). *Conditions and Reagents*: *ii* = AcOH, reflux, N_2, 20 h.

Furthermore, a report displayed (Figure 3) the synthesis of a hexacyclic (lactonamycin) via condensation of an enone derivative (**5**) with a thioester derivative (**6**) to produce the protected lactonamycin (**7**), which was subjected to hydrogenolysis to form lactonamycin (**8**).[xiii]

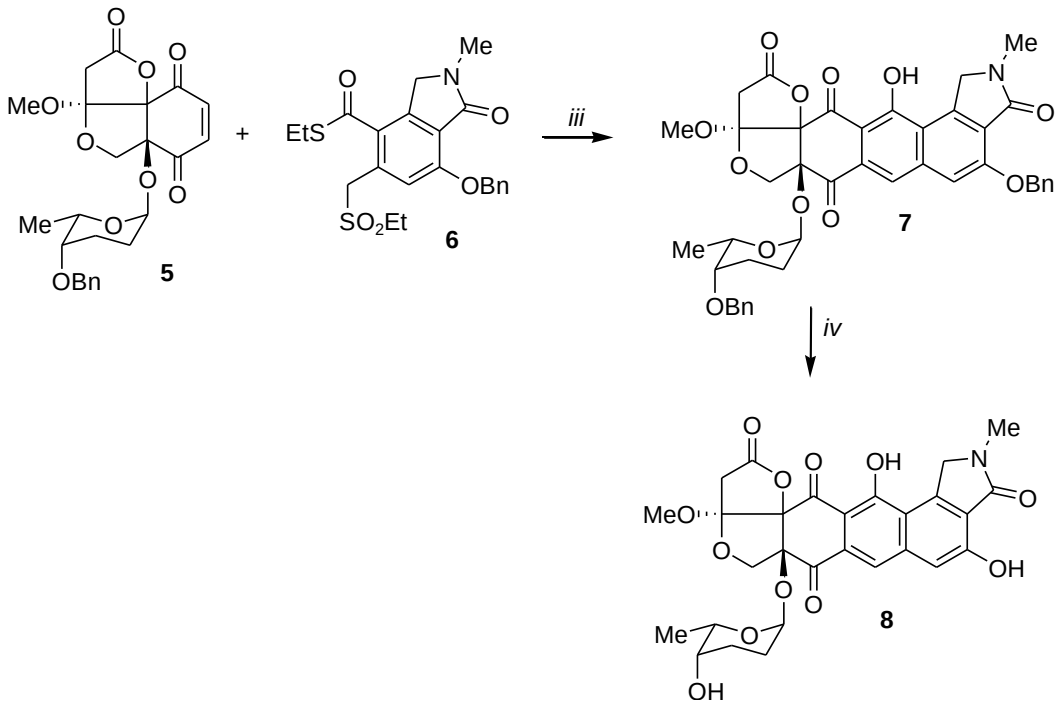

Figure 3. Synthesis of lactonamycin (**8**). *Conditions and Reagents*: *iii* = Potassium bis(trimethylsilyl)amide, THF, reflux, 7 h; *iv* = H_2, Pd-black, THF, rt, 10 min.

Other data indicates the reaction of 16-dehydropregnenolone (**9**) with methyl 5,5-dioxo-4,6-dihydropyrazolo[1,5-c]thiazole-2-carboxylate (**10**) to form two isomer such as methyl (1*S*,2*R*,7*S*,10*R*,11*S*,14*S*,15*S*,23*R*)-7-acetoxy-15-acetyl-10,14-dimethyl-20,21-diazahexacyclo[12.10.0.0^{2,11}.0^{5,10}.0^{15,23}.0^{17,21}]tetracosa-4,17,19-triene-19-carboxylate (**11**) and methyl (1*S*,2*R*,7*S*,10*R*,11*S*,14*S*,15*S*,23*S*)-7-acetoxy-15-acetyl-10,14-dimethyl-17,18-diazahexacyclo[12.10.0.0^{2,11}.0^{5,10}.0^{15,23}.0^{17,21}]tetracosa-4,18,20-triene-19-carboxylate (**12**) using diffe-rent conditions (Table 1, Figure 4).[xiv]

Table 1. Conditions and reagents for synthesis of two hexacyclic derivatives (**11** and **12**).

Entry	Sulfone	Reaction Condition	Isolated yield (11:12)
1	2 equiv.	MW, 250 ^{o}C, 10 min	33% (78:22)
2	2.5 equiv.	MW, 250 ^{o}C, 10 min	46% (76:24)
3	3 equiv.	MW, 250 ^{o}C, 10 min	49% (85:15)

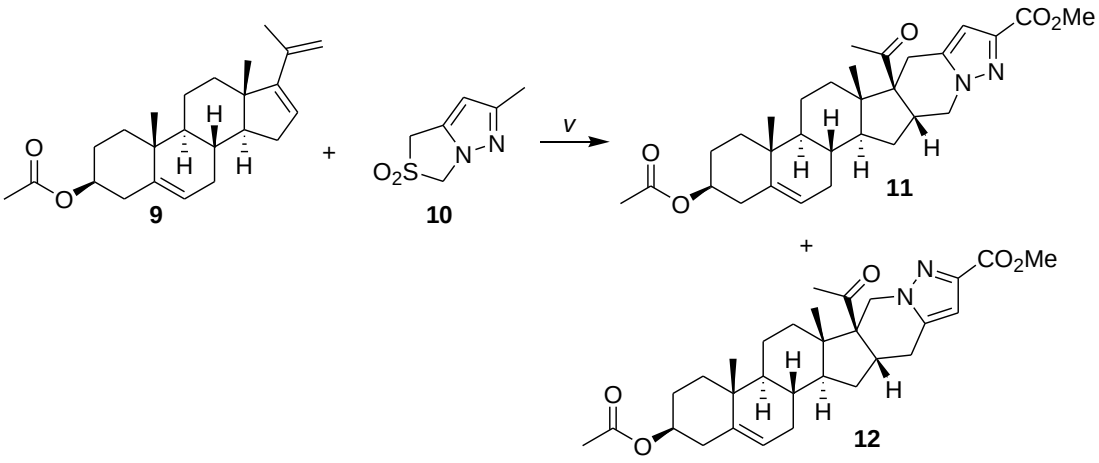

Figure 4. Synthesis of hexacyclic-steroids derivatives (**11** and **12**). *Conditions and Reagents*: *v* = MW, 250 ^{o}C, 10 min

Besides, a report showed the reaction of 2-bromobenzo[c]phenanthrene (**13**) with (4-vinylphenyl)methyl acetate (**14**) to form the compound [4-[(E)-2-benzo[c]phenanthrene-2-ylvinyl]phenyl]methyl (**15**) using palladium as catalyst. Subsequently, compound **15** was subjected to oxidative photocyclization to obtain coronen-1-yl acetate (**16**). Finally, the hexacyclic derivative coronen-1-ol (**17**) was prepared from **16** in the presence of sodium hydroxide (Figure 5).[xv]

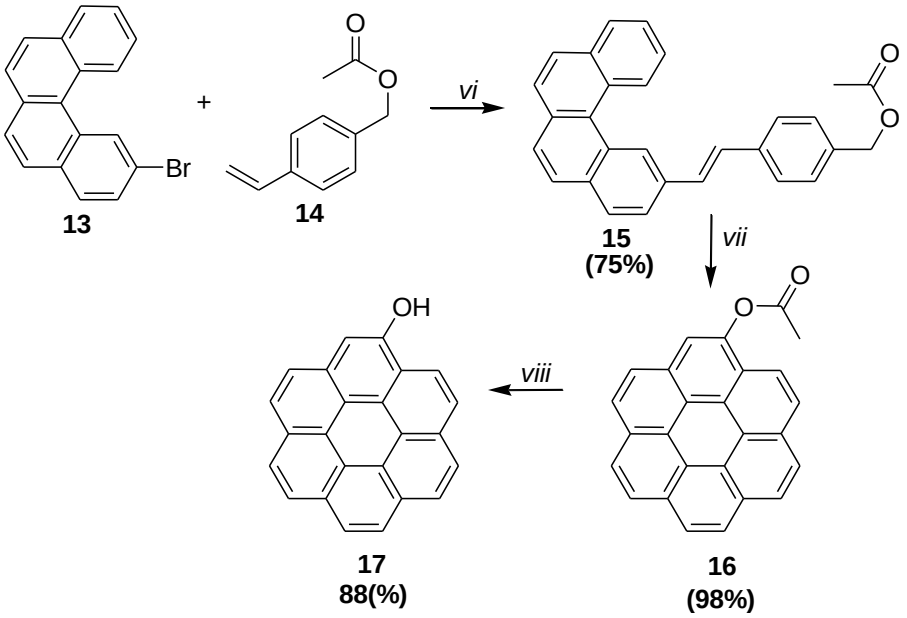

Figure 5. Synthesis of coronen-1-ol (**17**). *Conditions and Reagents*: *vi* = Pd, NaOAc, DMA, 140 °C; *vii* = *hν*, toluene, propylene oxide, I_2; *viii* = NaOH

Other data indicate the synthesis of (1*S*,15*R*,23*S*)-16-acetyl-3,11,14,16-tetrazahexacyclo-[12.10.0.0^{2,11}.0^{4,9}.0^{15,23}.0^{17,22}]tetracosa-2,4(9),5,7,17,19,21-heptaene-10,13-dione (**18**) from (1*R*,7*S*,9*S*)-16-acetyl-6-ethoxy-2,5,16-triazatetracyclo[7.7.0.0^{2,7}.0^{10,15}]hexadeca-5,10,12,14-tetraen-3-one (**17**) in the presence of anthranilic acid (Figure 6).[xvi]

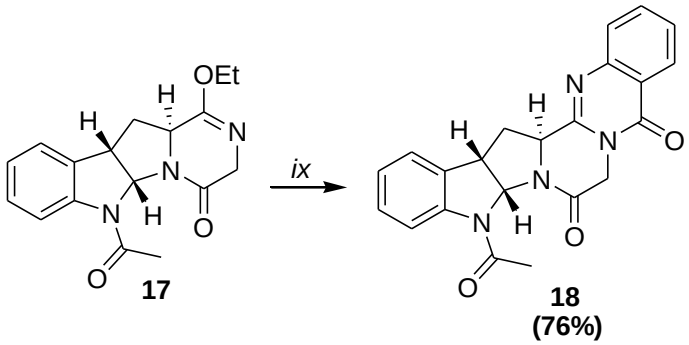

Figure 6. Synthesis of a hexacyclic derivative (**18**). *Conditions and Reagents*: *ix* = anthranilic acid, 140 °C, 4 h.

In addition, the hexacyclic derivative trimethyl-(3,3,13,13-tetraoctyl-16-trimethylsilyl-7,10,17,20-tetrathia-3,13-disilahexacyclo[9.9.0.02,9.04,8.012,19.014,18]icosa-1(11),2(9),4(8),5,12(19),14(18),15-heptaen-6-yl)silane (**20**) was prepared from the compound [4-bromo-5-[3,6-dibromo-5-(3-bromo-5-trimethylsilyl-2-thienyl)thieno[3,2-b]thiophen-2-yl]-2-thienyl]-trimethyl-silane (**19**) in the presence of dichlorodioctylsilane (Figure 7).[xvii]

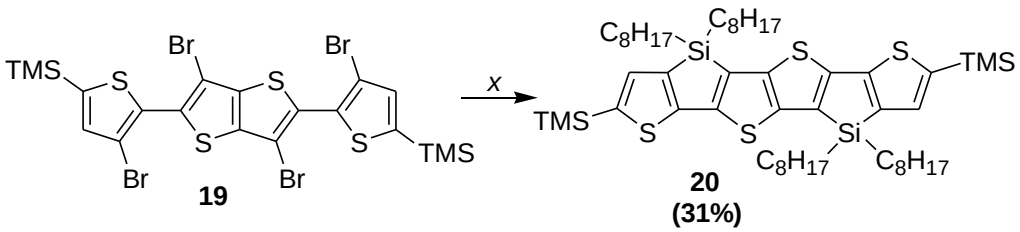

Figure 7. Synthesis of a hexacyclic derivative (**20**). *Conditions and Reagents*: *x* = *t*-BuLi, $(C_8H_{17})SiCl_2$, THF.

Other study (Figure 8) showed the cycloaddition of an amino-ester (**22**) analog to *O*-allyl salicylaldehyde (**21**) to form a tricyclic derivative as intermediary and subsequently to produce the hexacyclic derivative (**23**).[xviii]

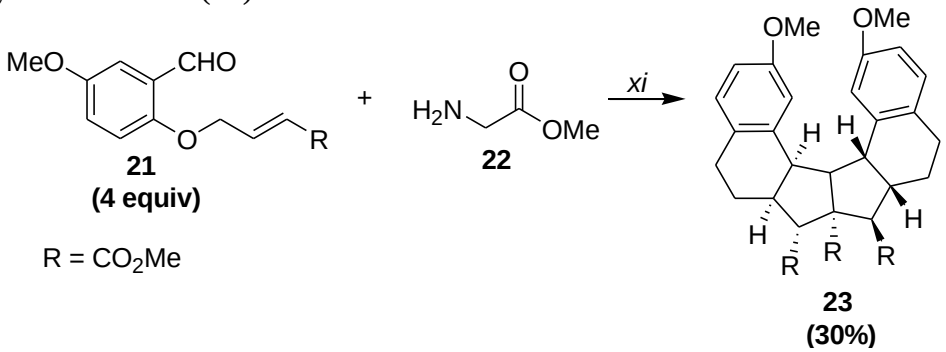

Figure 8. Synthesis of a hexacyclic derivative (**23**). *Conditions and Reagents*: *xi* = trimethylamine, toluene, 250 W, 150 °C, 10 min.

Other data (Figure 9) indicate that *β*-carbolinium salt reacted with an aldehyde derivative in the presence of a base to afford hexacyclic compound (**25**) according to the Knoevenagel mechanism.[xix]

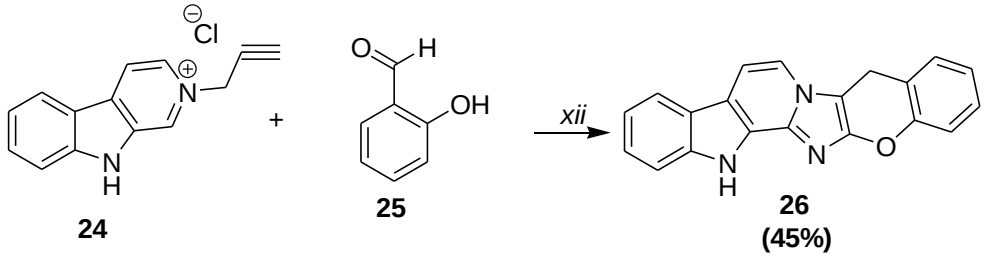

Figure 9. Synthesis of a hexacyclic derivative (**26**). *Conditions and Reagents*: *xii* = NH_4OAc, EtOH, MW 150 ^{O}C, 20 min

In addition, a study showed the preparation of a hexacyclic steroidal [(1'*S*,2'*S*,7'*S*,10'*R*,11'*S*, 14'*S*,15'*S*,16'*E*,23'*S*,24'*S*)-10',14'-dimethyl-16'-(p-tolylsulfonylimino)spiro[1,3-dioxolane-2, 21'-hexacyclo[12.11.0.$0^{2,11}$.$0^{5,10}$.$0^{15,24}$.$0^{18,23}$]pentacosa-4,17-diene]-7'-yl] acetate (**28**) from [(3*S*,8*R*,9*S*,10*R*,13*S*,14*S*)-10,13-dimethyl-17-[(*E*)-*C*-methyl-*N*-(p-tolylsulfonyl)carbonimidoyl]-2,3,4,7,8,9,11,12,14,15-decahydro-1*H*-cyclopenta[a]phenanthren-3-yl] acetate (**27**), 1,4-Dioxa-spiro[4.5]decan-8-one in the presence of pyrrolidine.[xx]

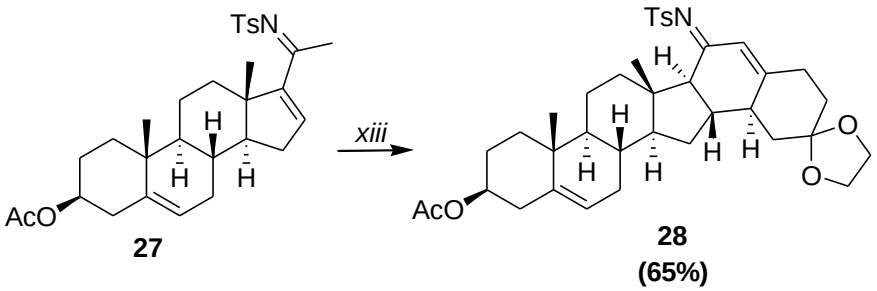

Figure 10. Synthesis of a hexacyclic-steroidal (**28**). *Conditions and Reagents*: *xiii* = 1,4-Dioxa-spiro[4.5]decan-8-one, pyrrolidine, MW 140 °C, 10 min.

On the other hand, a report displayed the cleavage of the Boc group involved in the chemical structure of methyl 2-[tert-butoxycarbonyl-[(2S,3R)-2-methyl-3-[(1S)-9-methyl-7-tricyclo [6.4.1.04, 13]trideca-4(13),5,7,9-tetraenyl]-5-oxo-pentyl]amino]acetate (**29**) through microwave irradiation. The authors suggest the formation of a cyclic azomethine ylide as an intermediary, which underwent intramolecular cycloaddition to give compound methyl (2S,3R,5R,6S,9S,10S, 13S)-2,6-dimethyl-8-azahexacyclo[11.6.1.02,10.03, 8.05,19.016,20] icosa-1(19), 16(20),17-triene-9-carboxylate (**30**).[xxi]

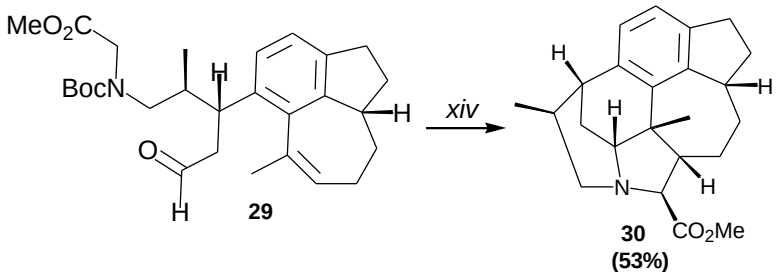

Figure 11. Synthesis of (−)-Daphenylline (**30**). *Conditions and Reagents*: *xiv* = NaOAc, 3,5-di-*tert*-butyl-4-hydroxytoluene, MS4A, toluene, microwave, 200 °C.

Other data (Figure 12) indicate the preparation of 4-(2-bromo-3-pyridyl)but-1-ynyl-triisopropyl-silane (**32**) from 2-bromo-3-(bromomethyl)pyridine (**31**) and 1-(Triisopropyl-silyl)-1-propyne. Then, the compound triisopropyl-[4-[2-[2-[4-(4-triisopropylsilylbut-3-ynyl)-

3-pyridyl]-ethynyl]-3-pyridyl]but-1-ynyl]silane (**33**) was synthesized from **32** via Sonogashira reaction under Pd^0/CuI catalysis. Following, **33** was desilylated with tetrabuty-lammonium fluoride to provide the unprotected pyridotriyne **34**. Then, Cyclopentadienylcobalt dicarbonyl catalyzed a cyclotrimerization of **34** to form the tetrahydrodiazahelicene compound (**35**). Finally, **35** was subject to irradiation in the presence of MnO_2 to form the compound 4,21-diazapentacyclo[12.8.0.0^{2,11}.0^{3,8}.0^{17,22}]docosa-1(14),2(11),3(8),4, 6,9,12,15, 17,19,21-undecaene (**36**).[xxii]

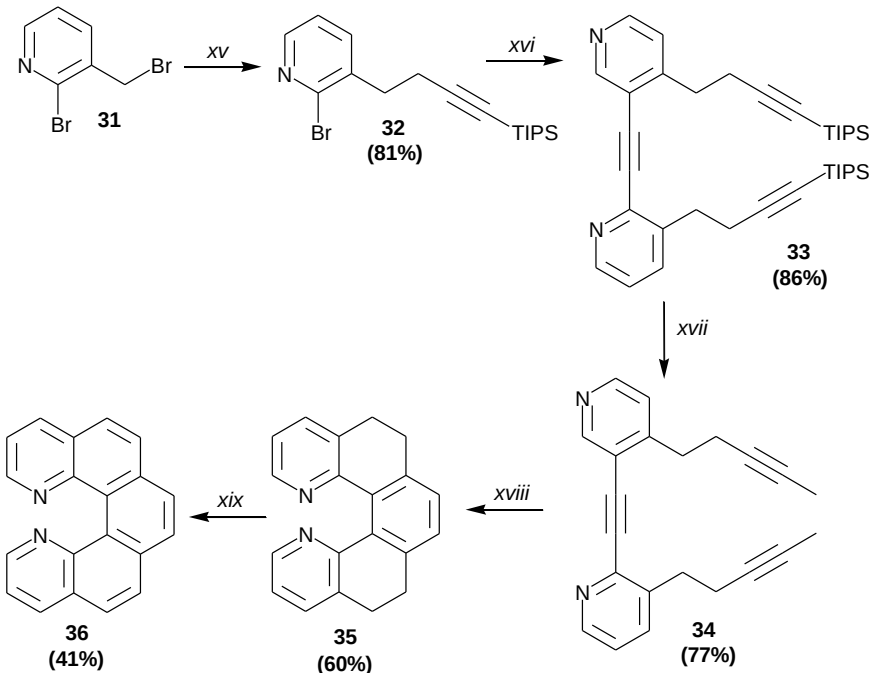

Figure 12. Synthesis of a hexacyclic derivative (**36**). *Conditions and Reagents*: *xv* = n-BuLi, THF, -78 ^oC, rt, 30 min; *xvi* = HC≡CH (gaseous), $Pd(PPh_3)_4$, CuI, piperidine, 80 ^oC, 30 min; *xvii* = nBu_4NF, THF, rt, 1 h; *xviii* = [$CpCo(CO)2$], PPh_3, decane, halogen lamp, 140 ^oC, 1 h; *xix* = MnO_2, toluene, microwave oven, 150 ^oC, 20 min. TIPS = triisopropylsilyl.

Besides, a study displayed the microwave-assisted cyclization of 1-(2-hydroxy-6-octyl-1-naphthyl)-6-octyl-naphthalen-2-ol (**37**) in the presence of $Cu(OAc)_2$ yielded the compound 6,15-dioctyl-12,22-dioxahexacyclo[11.7.1.1^{4,20}.0^{2,11}.0^{3,8}.0^{17,21}]docosa-1(20), 2(11),3(8),4,6, 9,13,15,17(21),18-decaene (**38**).[xxiii]

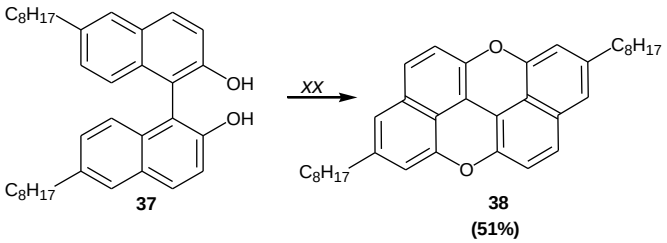

Figure 13. Synthesis of hexacyclic derivative (**38**). *Conditions and Reagents*: *xx* = $Cu(AC)_2$, pyridine, O_2, ODCB.

Other data showed the preparation of two hexacyclic analogs from a tetrahydro-β-carboline derivative via microwave-assisted intramolecular reaction.[xxiv]

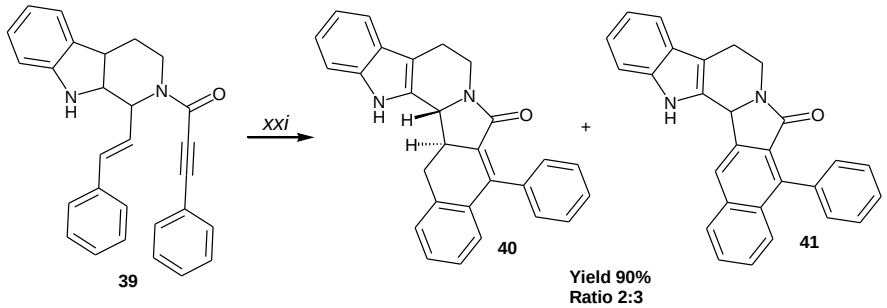

Figure 14. Synthesis of hexacyclic derivatives (**40 and 41**). *Conditions and Reagents*: *xxi* = tetrahydro-β-carboline derivative, MW, toluene, 170 °C, 15 min.

CONCLUSIONS

This review show several reaction protocols for the synthesis of hexacyclic derivatives, which involve conventional and non-conventional methods, in particular the use of different solvents and microwave irradiation conditions. It is noteworthy that this data can be used to make decisions in the development of new hexacyclic derivatives.

ACKNOWLEDGEMENTS

None

CONFLICT OF INTEREST

The authors declare no conflict of interest

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