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REVIEW OF MICROWAVE-ASSISTED SYNTHESIS OF AZIRINE AND AZETIDINE DERIVATIVES

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ABSTRACT
For several years, the synthesis of various heterocyclic derivatives has aroused great interest in the organic chemistry field. However, some reactions require special conditions and involve low yields. In the search for new chemical tools, some non-conventional methods involve energy sources, such as microwave irradiation. In this way, microwave-assisted synthesis has been used to prepare some azirine and azetidine derivatives. Analyzing these data, the aim of this research was to characterize the synthesis of azirine and azetidine derivatives using microwave irradiation.

KEYWORDS. Synthesis, azarine, azetidine, derivatives.

INTRODUCTION
For several years, interest in the synthesis of heterocyclic derivatives has increased in the organic chemistry field.[i-iv] In this way, some azetidine and azirine derivatives have been synthesized using conventional methods, which require different catalysts and special conditions.[v-viii] For example, a study showed the preparation of a azetidine analog (ethyl (1*R*)-3,3-dimethyl-2-(*N*-phenylanilino)-4-(*p*-tolylsulfonylamino)cyclobutanecarboxylate) from ethyl (2*R*)-2-(benzhydrylamino)-4-chloro-4-methyl-3-(p-tolylsulfonylamino)pentanoate (Figure 1). The reaction occurs by activation of chloride group with trimethylamine, followed by a cyclization to form an azetidine ring (Figure 1).[ix]

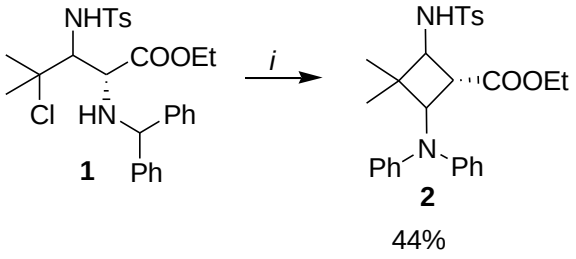


Figure 1. Synthesis of alkyl 3-aminoazetidine-2-carboxylate derivative (**2**). *Conditions and reagents*: *i* = (2*R*)-2-(benzhydrylamino)-4-chloro-4-methyl-3-(p-tolylsulfonylamino)pentanoate (**1**), trimethylamine, acetonitrile, 70 °C, 20 h.

Another report (Figure 2) displayed the preparation of a 2-substituted azetidine from a sulfinamido-alcohol derivative in the presence of Tsunoda reagent (cyanomethylenetributylphosphorane) via intramolecular cyclization.[x]

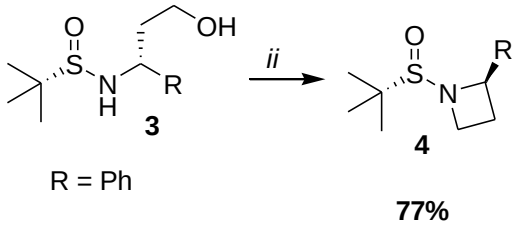


Figure 2. Preparation of (2*R*)-1-(1,1-dimethylethylsulfinyl)-2-phenyl-azetidine (**4**). *Conditions and reagents*: *ii* = Sulfinamido-alcohol derivative (**3**), Tsunoda reagent, toluene, scaled tube, 110 °C.

Yadav and colleagues (2008), showed that compound 3-Hydroxy-2-oxo-3-phenyl-propionitrile was subjected to aza-Michael addition in the presence of sodium hydride, followed by intramolecular cyclization to produce an azetidine derivative (Figure 3).[xi]

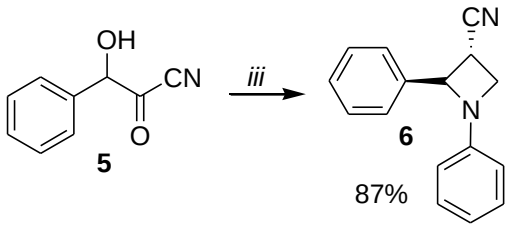


Figure 3. Synthesis of 1,2-Diphenyl-azetidine-3-carbonitrile (**6**). *Conditions and reagents*: *iii* = N-arylphospho-ramidate (**5**), sodium hydride/benzene, 60 °C, 20 min.

Other data (Figure 4) indicate the preparation of an enantiomerically pure substituted N-to-sylazirine derivative (2-benzyl-1-(p-tolylsulfonyl)aziridine) from (*S*)-*N*-tosylphenyl-alaninol. The conditions of this reaction permit a high yielding route for the synthesis of enantiopure N-Ts aziridines.[xii]

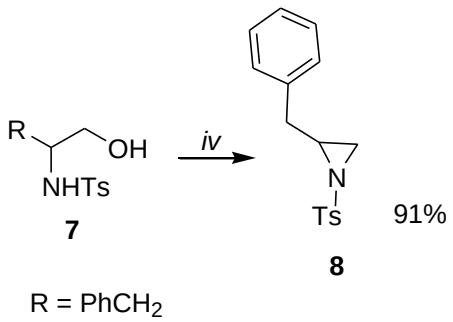


Figure 4. Preparation of N-tosylazirine derivative (**8**). *Conditions and reagents*: *iv* = (*S*)-*N*-tosylphenylalaninol (**7**), dichlorometane, tosyl chloride, 4-dimethylpyridine, trimethylamine, under argon, rt.

Another report (Figure 5) showed the reaction of a vinyl-selenone with a primary amine to form an aziridine derivative via an aza-Michael addition reaction, using toluene as a solvent; however, this reaction was significantly accelerated in water.[v]

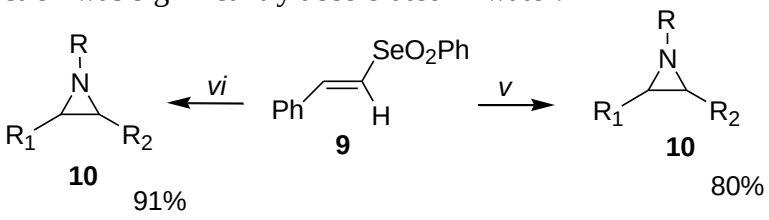


Figure 5. Synthesis of 1-benzyl-2-phenyl-aziridine (**10**). *Conditions and reagents*: *v* = [(*E*)-2-phenylselenonylvinyl]benzene (**9**), Benzylamine, toluene, 4Å molecular sieves, rt; *vi* = [(*E*)-2-phenylselenonylvinyl]benzene (**9**), Benzylamine, toluene, water, rt.

Furthermore, a study displayed the aziridination of a vinyl ketone (Figure 6) using SES-N3 (2-(trimethylsilyl)ethanesulfonyl-N3) reagent in the presence of the Ru(CO)-salene complex, which can provide aziridinyl-ketone formation (Figure 6).[xiii]

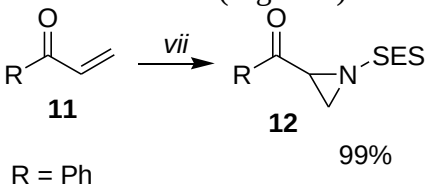


Figure 6. Phenyl-[1-(2-trimethylsilanyl-ethanesulfonyl)-aziridin-2-yl]-methanone (**12**). *Conditions and reagents*: *vii* = 1-Phenyl-propenone (**11**), CH_2Cl_2, MS, SES-N_3, 25 ^oC, N_2, 24 h.

All these data indicate that several azirine and azetidine derivatives have been synthesized using different protocols that require the use of some catalysts, and special conditions. In the search for new chemical tools to synthesize several heterocyclic derivatives, some non-conventional methods have been used, such as microwave-assisted reactions, which can increase reaction times and yield. For example, a study showed the synthesis of an azirine derivative (2-methyl-3-phenyl-2H-azirine) by microwave irradiation of compound [(Z)-1-azidoprop-1-enyl]benzene (Figure 7). This study indicates that the reaction route does not involve any solvent and that it can be used for non-terminal vinyl azides by applying microwave irradiation.[xiv]

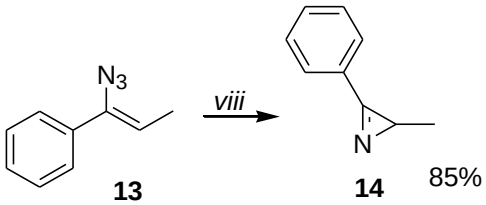


Figure 7. Synthesis of 2-methyl-3-phenyl-2H-azirine (**14**). *Conditions and reagents*: *viii* = 3-Azido-1,3-diphenyl-propenone (**13**), microwave irradiation, solvent free conditions.

Another study showed the reaction of 1-Azido-3-(1,3-diphenyl-allyloxy)-propan-2-ol with triphenylphosphine, which was subjected to microwave irradiation to aziridine-ring formation involved in the compound 2-(1,3-Diphenylallyloxy)methylaziridine. (Figure 8).[xv]

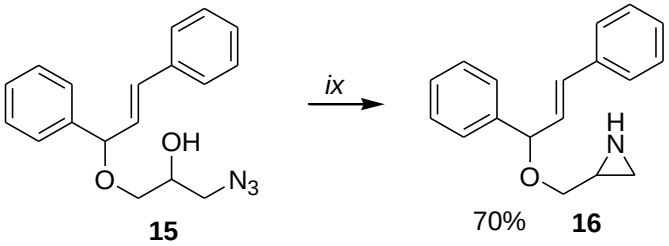


Figure 8. Preparation of aziridine derivative (**16**). *Conditions and reagents*: *ix* = 1-Azido-3-(1,3-diphenyl-allyloxy)-propan-2-ol (**15**) with triphenylphosphine, Ethanol, microwave irradiation,

In addition, a study showed that photolysis of 3-Azido-buta-1,2-diene produces the compound 2-methylene-2H-azirine (**18**). Then, **18** reacts with cyanide in chloroform to give the azirine corresponding (**19**). However, the authors indicate that the yield of methyleneazirine is limited by a photochemical secondary reaction leading to the formation of compounds **20** and **21** (Figure 9).[xvi]

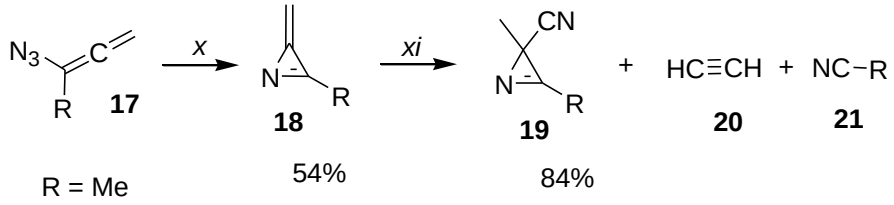


Figure 9. Synthesis of aziridine derivative (**19**). *Conditions and reagents*: *x* = Photoysis, 0 ^{o}C; *xi* = Photoysis, acetonitrile, chloroform.

Fowler (1971) indicates that azidostyrene can be subjected to irradiation with 3650 A light in a nitrogen atmosphere to form an azirine derivative (58).[xvii]

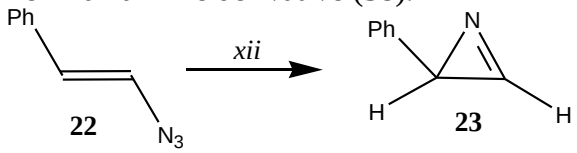


Figure 10. Synthesis of azerine derivative (**23**). *Conditions and reagents*: *xii* = [(*E*)-2-azidovinyl]benzene (**22**), nitrogen atmosphere, -50 ^{o}C.

Another report indicates that a bis-nitrone derivative was subjected to microwave irradiation to form a bis-isoxazoline analog. Then, a bis-aziridine derivative was produced by Baldwin rearrangement reaction of bis-isoxaline.[xviii]

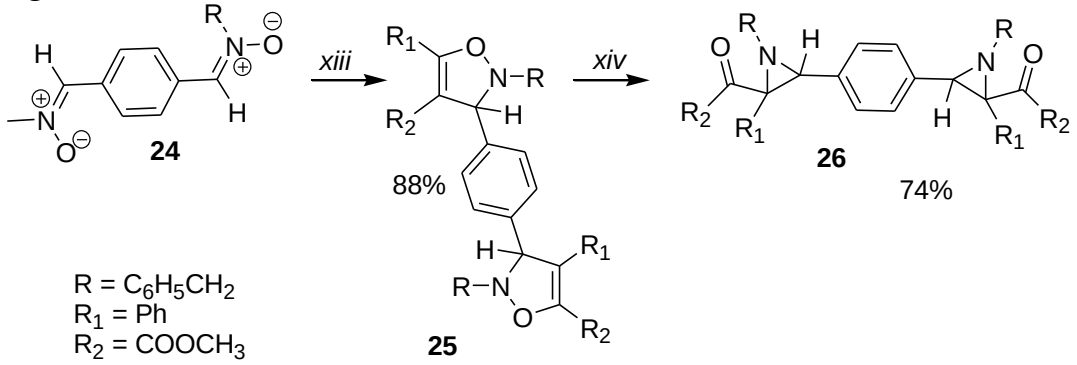


Figure 11. Synthesis of a bis-aziridine derivative (**26**). *Conditions and reagents: xiii* = bis-nitrone (**24**), dimethyl acetylene dicarboxylate, acetonitrile, 15°C, 5 min. microwave irradiation (400W); *xiv* = bis-isoxazoline (**25**), acetonitrile, 130 ^{o}C, 5 min, microwave irradiation (400W).

Furthermore, another study indicates the synthesis of N-Methyl-N-phenyl-2-phenyl-3H-azirin-3-carboxamide (**28**) from 3-Phenyl-5-(1-phenyl-ethyl)-isoxazole by microwave

irradiation using a mercury lamp (Philips HPK 125W). This reaction shows the opening of the oxazole ring and the formation of an azirine derivative.[xix]

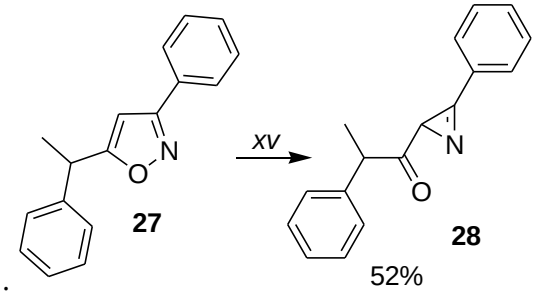


Figure 12. Synthesis of azirine derivative (**28**). *Conditions and reagents: xv* = 3-Phenyl-5-(1-phenyl-ethyl)-isoxazole (**27**), microwave irradiation (12W), 1h.

On the other hand, several azetidines have been synthesized via microwave-assisted reactions; for example, a study displayed the irradiation of 2-(N'-Benzylidene-hydrazino)-1-carbazol-9-yl-ethanone (**29**) in the presence of chloroacetyl chloride and trimethylamine to form the compound 1-(2-Carbazol-9-yl-2-oxo-ethylamino)-3-chloro-4-phenyl-azetidin-2-one (Figure 13).[xx]

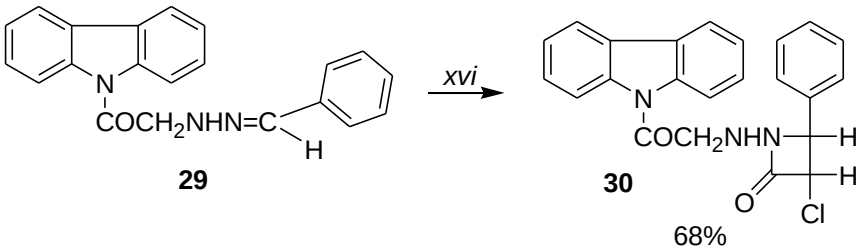


Figure 13. Synthesis of azirine analog (**30**). *Conditions and reagents: xvi* = chloroacetyl chloride, trimethylamine, microwave irradiation, 3 min.

Besides, an azetidine derivative (2-(3-benzoylphenyl)-N-(2-((3-chloro-2-oxo-4-phenylazetidin-1-yl)amino)-2-oxoethyl)propanamide was synthesized from (*Z*)-2-(3-benzoylphenyl)-N-(2-(2-benzylidenehydrazinyl)-2-oxoethyl)propane-mide in the presence of chloroacetylechloride and microwave irradiation.[xxi]

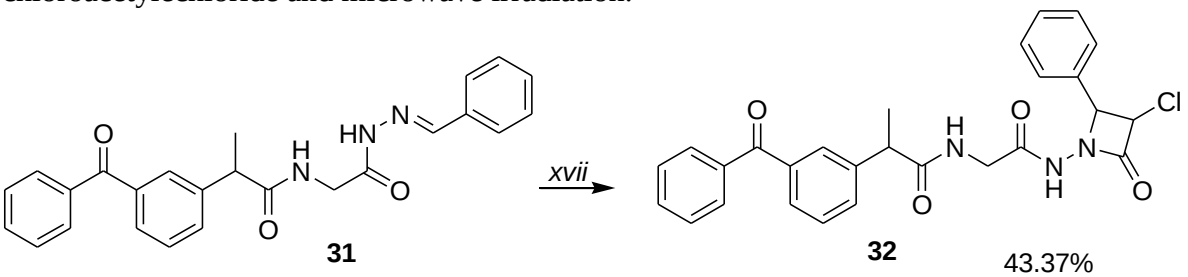


Figure 14. Synthesis of an azetidine derivative (**32**). *Conditions and reagents: xvii* = *Z*)-2-(3-benzoylphenyl)-N-(2-(2-benzylidenehydrazinyl)-2-oxoethyl)propane-mide (**31**), chloroacetylechloride, trimethylamine, microwave (MW 180), 8 min.

Another study displayed the reaction of N-(2-Bromobenzylidene)-5-[(4-methyl-4H-1,2,4-triazolyl)thiomethyl]-1,3,4-thiadiazol-2-amine with chloroacetyl chloride in the presence of trimethylamine. Then, the mixture was irradiated for 3 minutes to form the compound 4-(2-Bromophenyl)-3-chloro-N-[5-((4-methyl-4H-1,2,4-triazolyl)thiomethyl)-1,3,4-thiadia-zol-yl]-2-oxo-azetidine.[xxii]

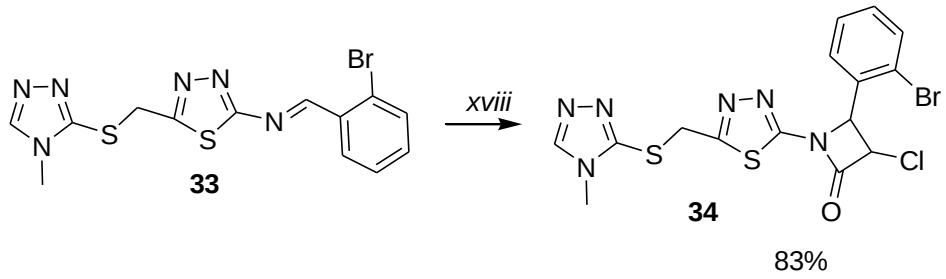


Figure 14. Synthesis of an azetidine analog (**34**). *Conditions and reagents: xviii* = N-(2-Bromobenzylidene)-5-[(4-methyl-4H-1,2,4-triazolyl)thiomethyl]-1,3,4-thiadiazol-2-amine (**33**), chloroacetyl chloride, triethylamine microwave irradiation, 3 min.[xv]

Another report showed that azadiene was irradiated for 20 minutes at 660 W to obtain two azetidinone derivatives. It is noteworthy that there was a higher yield of cis isomer (Figure 15).[xxiii]

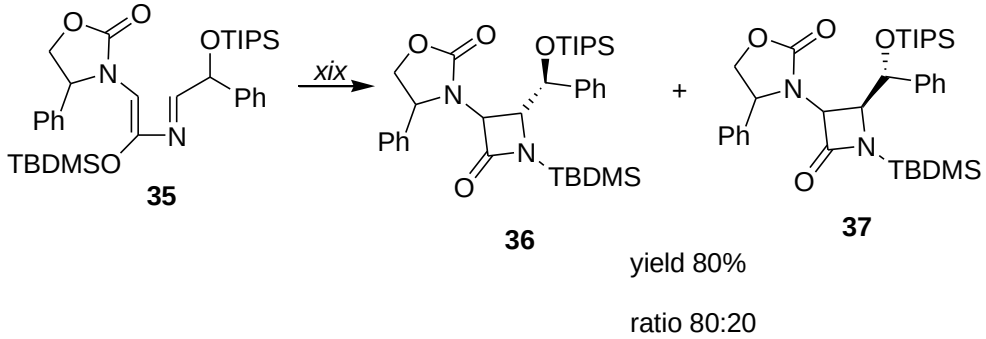


Figure 14. Synthesis of azetinone derivatives (**36** and **37**). *Conditions and reagents: ixx* = azadiene (**35**), microwave irradiation (660 W), 20 min.

Wessig and Schwarz (1998), displayed the influence of photo-irradiation on the diastereoselectivity in the synthesis of 2-azetidinones from ketenes and imines via the Staudinger reaction. In this way, two azetidine derivatives were prepared from 1-Diazo-3-phenylsulfanyl-propan-2-one and a nitro-benzylidene-iso-propylamine derivative under microwave irradiation.[xxiv]

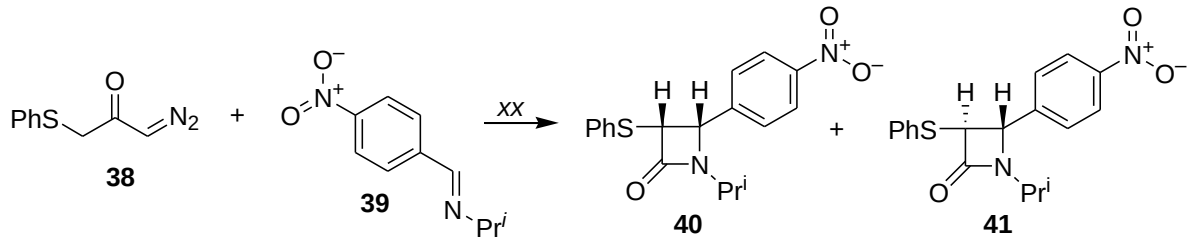


Figure 14. Synthesis of azetinone derivatives (**40** and **41**). *Conditions and reagents: xx* = 1-Diazo-3-phenylsulfanyl-propan-2-one (**38**), nitro- benzylidene iso-propylamine analog (**39**), microwave irradiation, 2 h.

Another study showed the reaction of the oxime with the Ir[dF(CF3)ppy]2(dtbbpy)PF6 complex assisted by microwave irradiation to form an azetidine derivative ((1*R*,5*S*)-6-methoxy-7-phenyl-3-oxa-6-azabicyclo[3.2.0]heptane).[xxv]

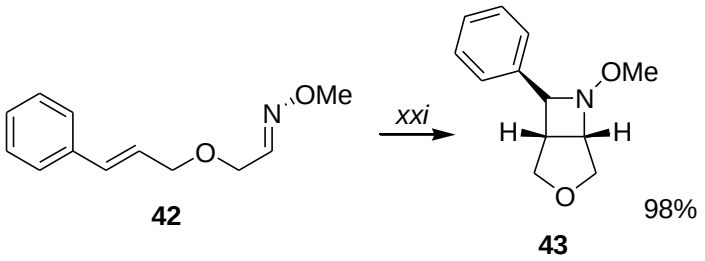


Figure 15. Synthesis of an azetinone analog (**43**). *Conditions and reagents: xxi* = microwave irradiation (427 W), THF, 0.5 h.

Besides, a report indicates the reaction of *N*-(4-nitrobenzylidene)-4-methoxyaniline (**44**) with 2-chloroacetyl chloride under microwave irradiation to form two azetidine derivatives.[xxvi] It is important to mention that this reaction was carried out without any catalyst agent (Figure 16).

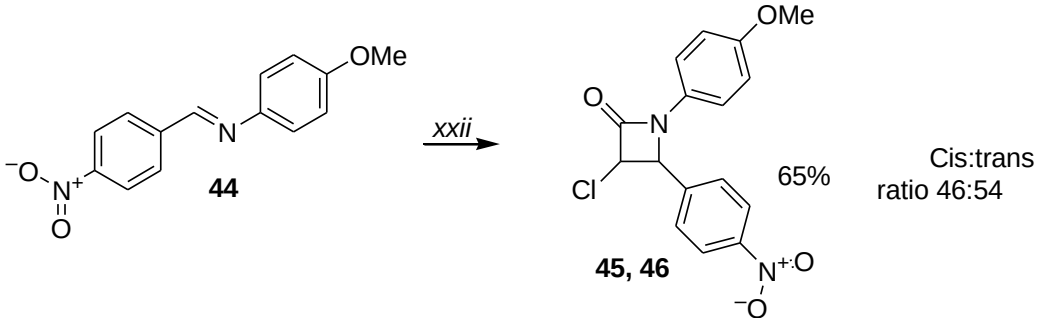


Figure 16. Synthesis of 3-Chloro-1-(4-methoxy-phenyl)-4-(4-nitro-phenyl)-azetidin-2-oneazetinone derivatives (**45** and **46**). *Conditions and reagents: xxii* = *N*-(4-nitrobenzylidene)-4-methoxyaniline and 2-chloroacetyl chloride, trimethylamine, dimethylformamide,150 mw 180 min.

Other studies indicate the synthesis of an azetidine analog (**50**) using a multicomponent system (isonicotinic acid hydrazide (**47**), aldehyde derivative (**48**) and 2,3-Dihydro-furan (**49**)) in the presence of montmorillonite k-10 under irradiation.[xxvii]

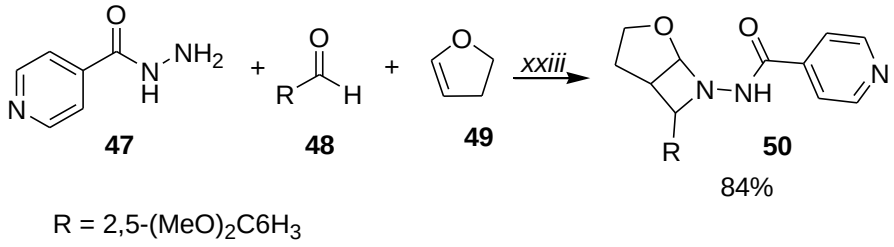


Figure 17. Synthesis of an azetidine derivative (**50**). *Conditions and reagents: xxii* = montmorillonite k-10, acetonitrile, acetonitrile, microwave irradiation 70 ^{o}C. 49 min.

Dandia and colleagues (2003), displayed the synthesis of an azetidine analog from a 3-arylimino indolinone derivative and chloroacetyl chloride under solvent-free conditions using K_2CO_3-Al_2O_3 system as support under microwave irradiation (Figure 18).[xxviii]

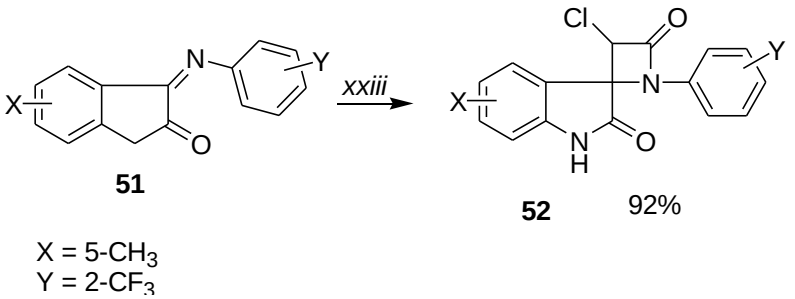


Figure 18. Synthesis of an azetidine derivative (**50**). *Conditions and reagents: xxiii* = chloroacetyl chloride, K_2CO_3-Al_2O_3, microwave irradiation, 172 ^{O}C.

Furthermore, Burkett (2009) showed the synthesis of 3-(N-substituted ammonio)propyl sulfate (**54**) by ring opening of compound tetrahydro-thiopyran 1,1-dioxide (**53**) in the presence of acetonitrile. Then, 54 was subjected to microwave irradiation under basic conditions to form an azetidine derivative (**55**).[xxix]

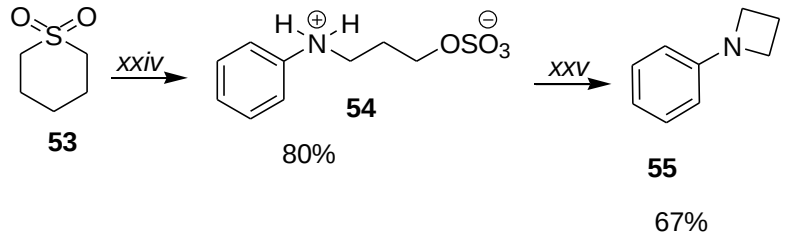


Figure 19. Synthesis of 1-Phenyl-azetidine (**55**). *Conditions and reagents: xxiv* = acetonitrile, 80 ^{o}C, 90 min; *xxv* = potassium hydroxide, water, microwave irradiation, 150 ^{o}C, 15 min.

Besides, other studies indicate that anti-N-sulfonylaziridine (56) is an excellent substrate for an azetidine derivative (trans-3-(N-tosylamino)azetidine-2-carboxylate) formation under microwave conditions (Figure 20).[xxx]

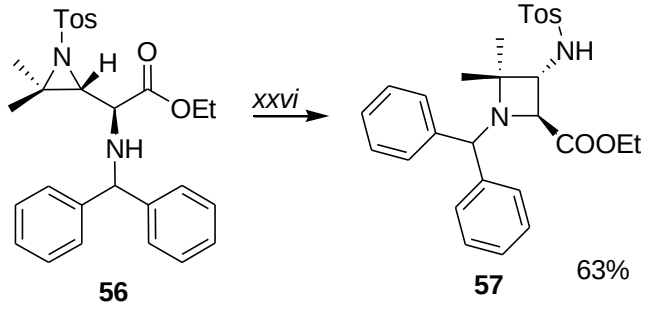


Figure 20. Synthesis of 3-(N-tosylamino)azetidine-2-carboxylate (**57**). *Conditions and reagents: xxvi* = acetonitrile, microwave irradiation, 120 °C, 10 min.

Another study indicates the preparation of 4-(3-Bromophenyl)-1-(3,4,5-trimethoxyphenyl)-3-(2-thienyl)azetidin-2-one (**60**) from *N*-(3-bromobenzylidene)-3,4,5-trimethoxybenzena-mine (**58**) and acyl chloride (**59**) under assisted-irradiation (Figure 21).[xxxi]

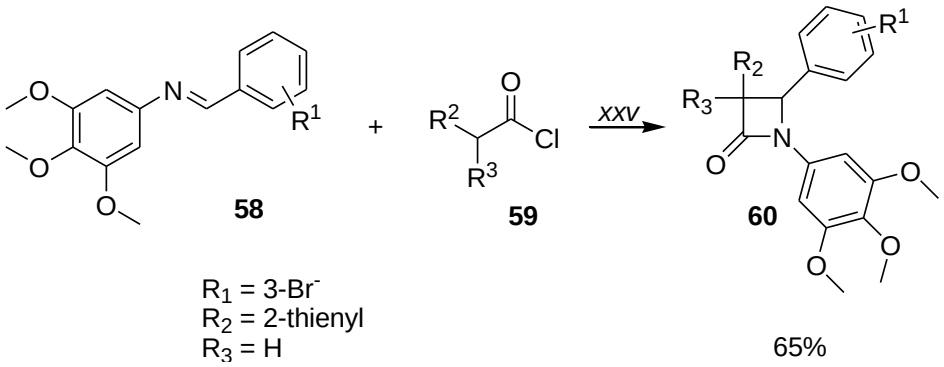


Figure 21. Synthesis of an azetidine derivative (**59**). *Conditions and reagents: xxvi* = triethylamine, microwave irradiation, 80 °C, 10 min.

Besides, Banik and cols (1992), showed the synthesis of an azetidine analog (**62**) from an imine derivative (**61**) and benzyloxyacetyl chloride under microwave irradiation.[xxxii]

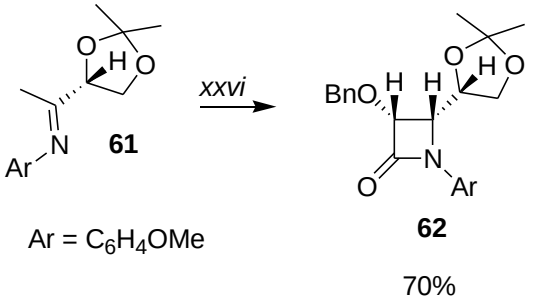


Figure 22. Synthesis of an azetidine derivative (**62**). *Conditions and reagents: xxvi* = imine derivative (**61**) benzyloxyacetyl chloride, triethylamine, microwave irradiation, 80 °C, 3 min.

Maruyama and colleagues (1981), displayed the photochemical reaction of cis-N-methyl-3,5-bis(methoxycarbonyl)cyclopentane-1,2-dicarboximide (**63**) to form an azetidine deriva-tive (Figure 23). These studies indicate that irradiation of **63** produces ring contraction of the pyrrolidine-2,5-dione ring to form an azetidine derivative (**64**).[xxxiii]

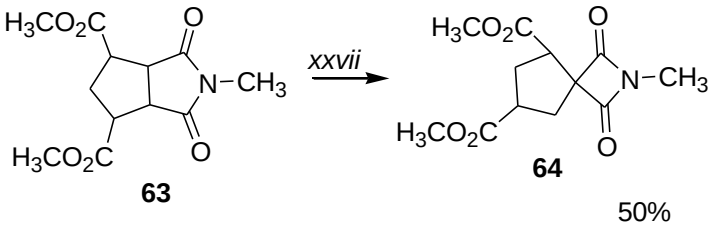


Figure 23. Synthesis of an azetidine derivative (**64**). *Conditions and reagents: xxvii* = cis-N-methyl-3,5-bis(methoxycarbonyl)cyclopentane-1,2-dicarboximide (**63**), microwave irradiation (254W).

Besides, another report indicates that compound 2-[(Benzyloxycarbonyl)(methyl)amino]-3-[(dimethyl)(1,1,2-trimethylpropyl)silyloxy]-1-phenylpropan-1-on (**65**) was subjected to irradiation to form the compound (2*S*,3*S*)-2-[[dimethyl(1,1,2-trimethylpropyl) silyl]oxymethyl]-3-phenyl-azetidin-3-ol (**67**). In this study, the reaction mechanism suggests that an excited carbonyl group extracts an H atom from the N-Me group, producing an intermediate (**66**) followed by ring closure to form azetidine derivative.[xxxiv]

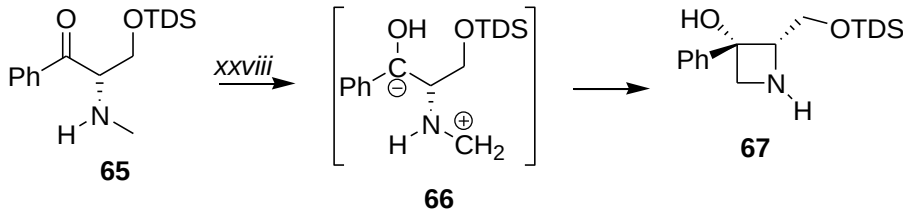


Figure 24. Synthesis of an azetidine analog **(67).** *Conditions and reagents: xxviii* = cyclo-hexane, microwave irradiation.

Another study indicates that 2,5-Diphenyl-[1,3,4]oxadiazole was subjected to intermolecular [2 + 2] photocycloaddition with indene to form an azetidine derivative under ultraviolet light irradiation.[xxxv]

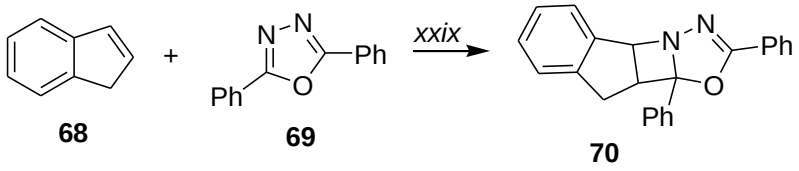
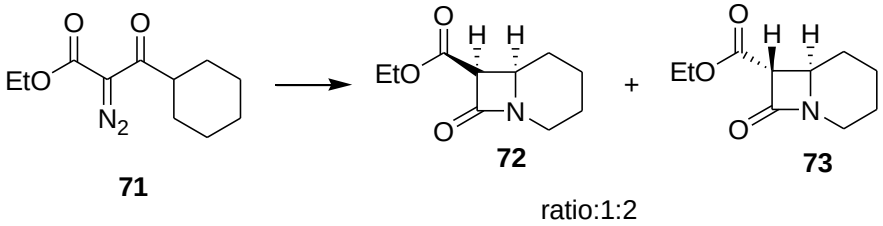


Figure 25. Preparation of an azetidine derivative **(70).** *Conditions and reagents: xxix* = indeno (**68**), 2,5-Diphenyl-[1,3,4]oxadiazole (**69**) K_2CO_3-Al_2O_3, ultraviolet light irradiation.

Finally, a study showed the photodecomposition of N-[(Ethoxycarbonyl)diazoacetyll-piperidine (**71**) to form a mixture of cis and trans-azetidine derivatives in 80% yield.[xxxvi]



ratio:1:2

Figure 26. Synthesis of cis- and truns azetidine **(71, 72).** *Conditions and reagents: xxix* = N-[(Ethoxycarbonyl)diazoacetyll-piperidine (**71**) carbon tetrachloride, irradiation (medium-pressure mercury lamp, room temperature.

CONCLUSIONS

This review describes the microwave-assisted synthesis of several azirine and azetidine derivatives that are of great interest in the field of organic chemistry. These protocols involve the use of some energy sources such as microwave radiation. It is noteworthy that the use of microwave irradiation involves short reaction times and high yields.

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CONFLICT OF INTEREST

Authors declare that there is no conflict of interests regarding the publication of the paper in this study

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