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# REVIEW ON THE MICROWAVE-ASSISTED SYNTHESIS OF SOME BENZO AND DIBENZOAZEPINE DERIVATIVES

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## ABSTRACT
In the literature there are several methods for the synthesis of different benzo- and dibenzoazepine derivatives; however, some reactions require special conditions and involve low yields. It is important to mention that some non-conventional methods that involve energy sources, such as microwave irradiation, have been used to prepare some benzo- and dibenzoazepine derivatives. The aim of this research was to characterize the synthesis of benzo- and dibenzoazepine derivatives using microwave-assisted.

**KEYWORDS**. Synthesis, benzoazepine, dibenzoazepine, microwave, derivatives.

## INTRODUCTION
For several years, there has been growing interest in the synthesis of new benzo- and dibenzoazepine derivatives in medicine and organic chemistry fields.[i-vi] It is noteworthy that some benzo- and dibenzoazepine derivatives have been developed using several conventional methods, which require different catalysts and special conditions.[vii-x] For example, a study showed the reaction of *o*-phenylenediamine with acetophenone in the presence of polyphosphoric acid (PPA) or $SiO_2$ at 40-50°C to form the compound 2,4-diphenyl-4-methyl-3H-5-hydro-1,5-benzodiazepine (Figure 1).

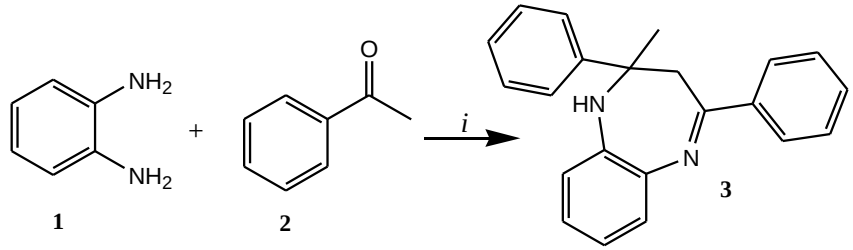


**Figure 1**. Synthesis of a benzodiazepine derivative (**3**). Reagents and conditions: *i* = *o*-phenylenediamine, PPA or $SiO_2$, at 4O-5O ºC, 5h.

The reaction mechanism proposed involves the amine of *o*-phenylenediamine attacking the carbonyl group. Following, a shift of the hydrogen-attached methyl group then occurs to afford an isomeric enamine, followed by an intramolecular cyclization to produce a seven-membered ring.[xi] Another report shows the synthesis of 2-Benzenesulfonylmethyl-1-methanesulfonyl-4-phenyl-1H-benzo[b]azepine from N-(1-Benzenesulfonylmethyl-vinyl)-N-(2-phenylethynyl-phenyl)-methanesulfonamide, (JohnPhos)Au(CH3CN)SbF6, and Et3N (Figure 2). The reaction mechanism proposed gold(I)-catalyzed regioselective cycloisomerization of N-(o-alkynylaryl)-N-vinyl sulfonamides to form a benzoazepine derivative.[xii]

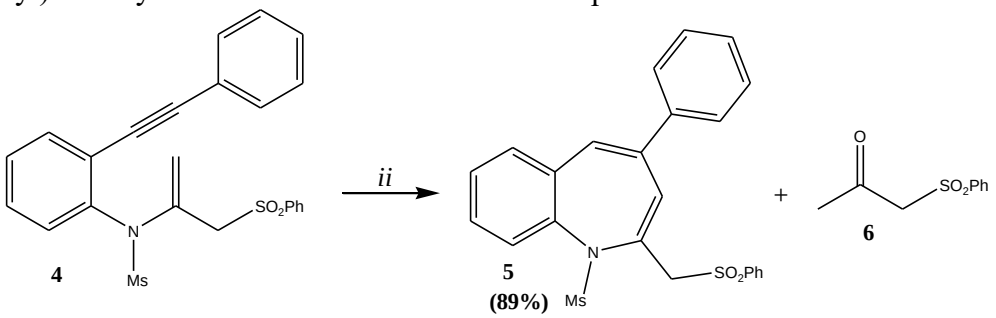


**Figure 2**. Synthesis of a benzoazepine analog (**5**). Reagents and conditions: *ii* = vinyl-methanesulfonamide derivative (**4**) (JohnPhos)Au($CH_3CN$)$SbF_6$, and $Et_3N$

Besides, a study displayed the reaction of 2-phenyl-1H-imidazole with 3-methylene-4-phenethyloxetan-2-one in the presence of [Cp*RhCl2]2 to form the compound 5-(2-phenylethyl)-5*H*-imidazo[2,1-a][2]benzazepine-6-carboxylic acid (Figure 3).[xiii]

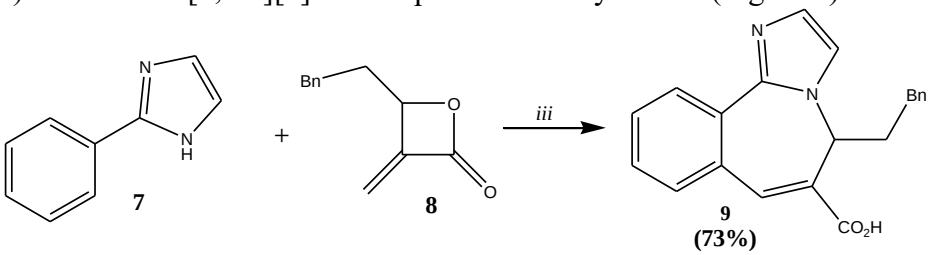


**Figure 3**. Synthesis of a benzoazepine derivative(**9**). Reagents and conditions: *iii* = 2-phenyl-1H-imidazole (**7**), oxetanone analog (**8**), [RhCp*Cl2]2, AgOAc, DCM, 100 $^{O}$C, 10 h.

Ghosh and co-workers (2008) reported ring-closing metathesis of diene using benzylidene bistricyclohexylphosphinorutenium(IV) dichloride (**10**) as a catalyst at room temperature to produce a benzazepine derivative (Figure 4).[xiv]

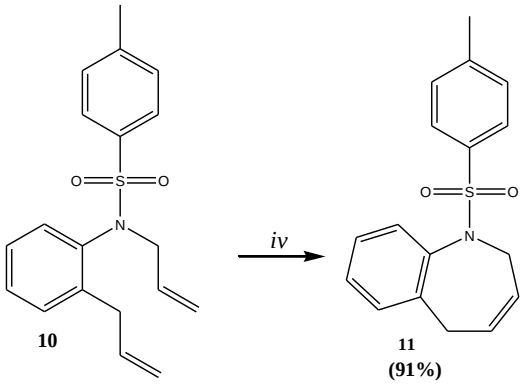


**Figure 4** Synthesis of a benzoazepine derivative (**11**). Reagents and conditions: *iv* = compound **10**, $CH_2Cl_2$, rt, 2–3 h.

Other data indicate the preparation of 1,4-benzodiazepine-2,5-dione. This synthesis employs a Ugi four-component condensation using a convertible isocyanide (1-isocyanocyclohexene), followed by an acid-activated cyclization reaction (Figure 5). The proposed mechanism involves the intermolecular formation of an imine from OPDA and dimedone, promoted by $Fe_3O_4$@chitosan; then, a seven-atom ring is formed via intramolecular cyclization.[xv]

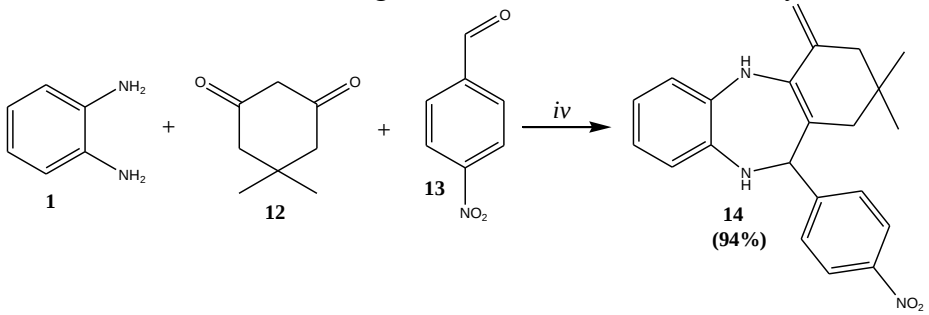


**Figure 5**. Synthesis of a dibenzoazepine derivative (**14**). Reagents and conditions: *v* = Benzene-1,2-diamine (**1**), 5,5-Dimethyl-cyclohexane-1,3-dione (**12**), 4-Nitro-benzaldehyde (**13**), $Fe_3O_4$@chitosan, EtOH, rt, 60 min.

Other study showed the reaction of an acrylamide-tethered styrene derivative (**15**) with Cyclohexanecarboxylic acid 2,5-dioxo-pyrrolidin-1-yl ester (**16**) in the presence of Ir(ppy)2(dtbbpy)PF6, to give a good yield (Figure 6).[xvi]

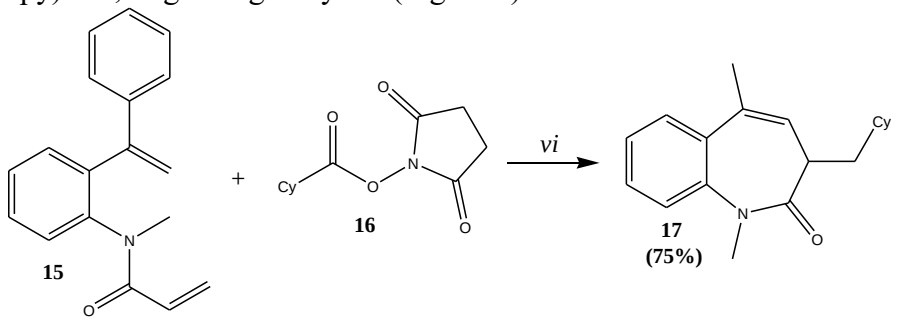


**Figure 6**. Synthesis of a benzoazepine derivative (**17**). *Reagents and Conditions*: *vi* = compound **15**, compound **16**, Ir(ppy)2(dtbbpy)PF6, $H_2O$, pyridine, MeCN, rt, 2*3 W blue LEDs overnight.

On the other hand, it is important to mention that microwave-assisted methods have been used for the preparation of benzo- and dibenzazepine derivatives. In this way, a study displayed the synthesis of (*Z*)-1-Benzylidene-2-isobutyl-7,8-dimethoxy-3-(4-methoxybenzyl)-2,3,4,5-

tetrahydro-1*H*-benzo[*d*]azepine (Figure 7) from *N*-(2-Bromo-4,5-dimethoxyphenethyl)-*N*-(4-methoxybenzyl)-5-methyl-1-phenylhex-1-yn-3-amine (**18**). The proposed reaction mechanism involves a Pd-catalyzed intramolecular hydroxylation of acetylene group.[xvii]

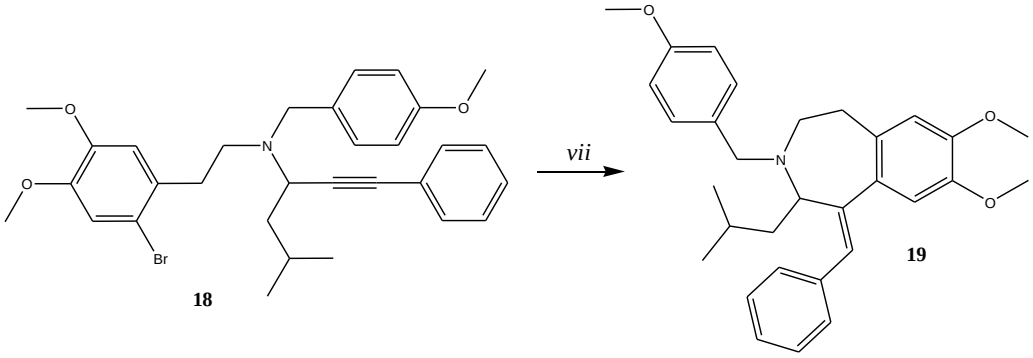


**Figure 7**. Synthesis of a benzoazocine derivative (**19**). *Reagents and Conditions*: *vii* = compound **18**, $Pd(PPh_3)_4$, HCOONa, DMF/$H_2O$, MW (100W), 15 min.

Other studies showed the synthesis of 1-Benzylidene-8-ethyl-4-hydroxymethyl-3-methyl-1,3,4,5-tetrahydro-benzo[d]azepin-2-one from an amide derivative in the presence of Herrmann'S palladacycle reagent using microwave-assisted Heck reductive cyclization (Figure 8).[xviii]

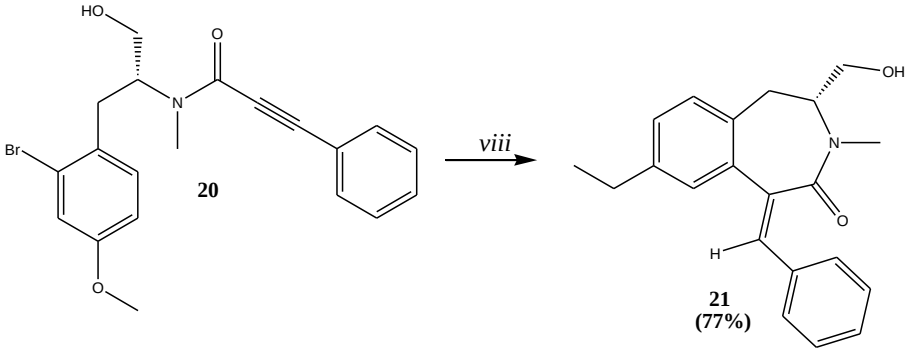


**Figure 8**. Synthesis of a 3-Benzazepine analog (**21**). *Reagents and Conditions*: *viii* = amide derivative (**20**), Hermann's palladacycle, $HCO_2Na$, 110 °C, 20 min, MW.

Besides, a report indicates the reaction of a keto acid derivative with benzylamine to form the compound 4-Methyl-3-phenyl-1,3-dihydro-benzo[d]azepin-2-one under microwave irradiation (Figure 9).[xix]

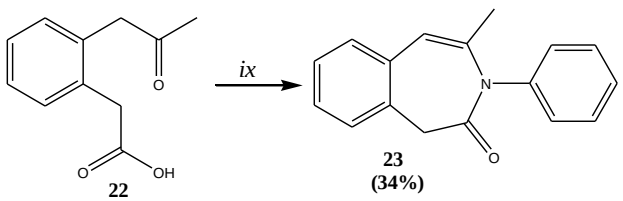


**Figure 9**. Synthesis of a 3-benzazepinone derivative (**23**). *Reagents and Conditions*: *ix* = [2-(2-Oxo-propyl)-phenyl]-acetic acid (**22**), benzylamine, toluene, MW 120 °C, 2-3 h.

Pozarentzi et al. (2002) describe the preparation of 2,7,8-Trimethyl-2,4-diphenyl-2,3-dihydro-1H-benzo[b][1,4]diazepine via condensation of acetophenone with phenyl-diamine derivative through microwave irradiation without solvent (Figure 10).[xx]

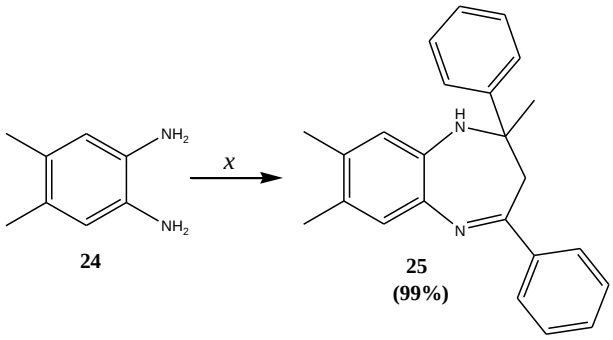


**Figure 10**. Synthesis of a benzodiazepine derivative (**25**). Reagents and reaction conditions. *x* = 4,5-Dimethyl-benzene-1,2-diamine (**24**), acetic acid, MW 80W, 2 min.

Besides, another study displayed the preparation of 2,2,4-trimethyl-2,3-dihydro-1H-benzo[b][1,4]diazepine form *o*-phenylenediamine (**1**) and acetone in the presence of $SiO_2/ZnCl_2$ under microwave irradiation.[xxi]

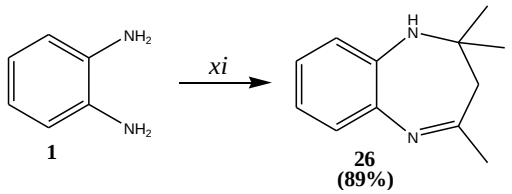


**Figure 11**. Synthesis of a benzodiazepine analog (**26**). *Reagents and reaction conditions: xi* = compound **1**, $SiO_2/ZnCl_2$, MW 50 $^{O}$C, 1 h.

Other data indicate that calcium-catalyzed synthesis of a benzazepine analog from benzenesulfonamide derivative (**27**). The authors indicate that the reaction occurs highly diastereoselectively under assisted-microwave conditions, yielding exclusively the trans-diastereomer (Figure 12).[xxii]

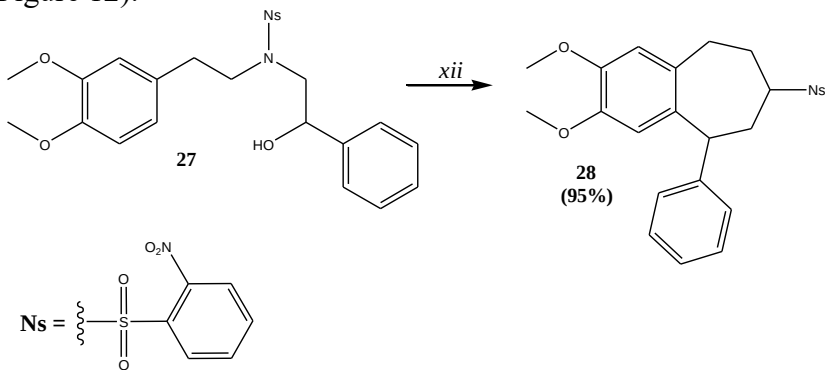


**Figure 12**. Synthesis of benzazepine derivative (**28**). *Reagents and reaction conditions*. *xii* = compound **27**, $Ca(NTf_2)_2$, DCE, 15 min, MW 100 °C.

In addition, a study showed the preparation of 7,8-Dimethoxy-3-(4-methoxy-benzyl)-1-(1-phenyl-ethylidene)-1,3,4,5-tetrahydro-benzo[d]azepin-2-one via reaction of But-2-ynoic acid [2-(2-bromo-4,5-dimethoxy-phenyl)-ethyl]-(4-methoxy-benzyl)-amide with phenyl-boronic acid using $Pd(PPh_3)_2Cl_2$ as a catalyst under microwave irradiation (Figure 13).[xxiii]

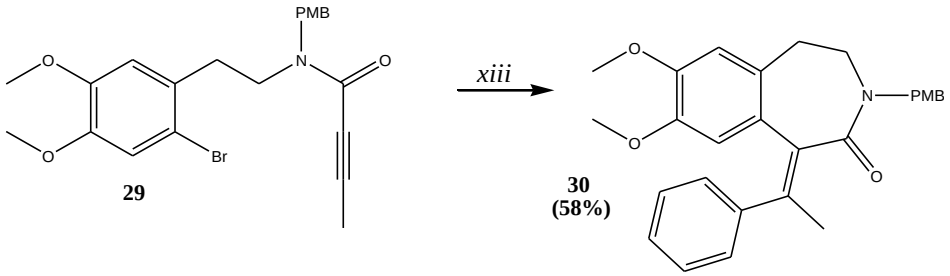


**Figure 13**. Synthesis of bezazepine-2-one derivative (**30**). *Reagents and reaction conditions*. *xiii* = propargylamide (**29**), $Pd(PPh_3)_2Cl_2$, MW 100 ºC, 15 min.

Other study showed the reaction of 2,3-diaminophenol with acetophenone (Figure 14) to form two products such as 6-Methyl-6,8-diphenyl-6,7-dihydro-5-oxa-9-aza-benzocyclohepten-1-ylamine (**33**) and 2-Methyl-2,4-diphenyl-2,3-dihydro-1H-benzo[b][1,4]diazepin-6-ol (**34**).[xxiv]

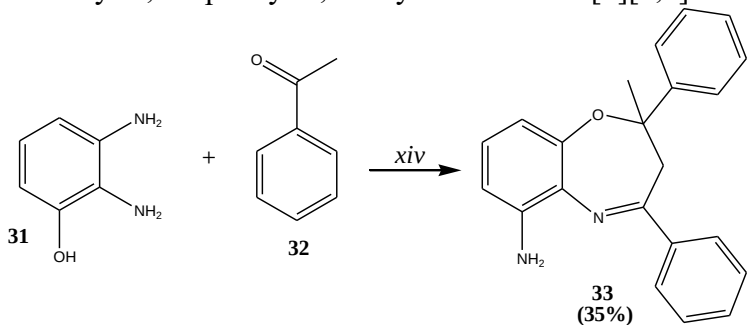


**Figure 14**. Synthesis of benzoxazepine (**33**) and hydroxyl-benzodiazepine derivatives (**34**). *Reagents and reaction conditions*. *xiv* = 2,3-diaminophenol (**31**), acetophenone (**32**), $CH_3COOH$, MW 80 ºC,

Quick and Wuensch (2015) displayed the intramolecular cyclization of a phenylacetamide (**35**) in the presence of HCl to produce the compound 2-[(1R)-1-Phenylethyl]-2,5-dihydro-2-benzazepin-1-one (Figure 15).[xxv]

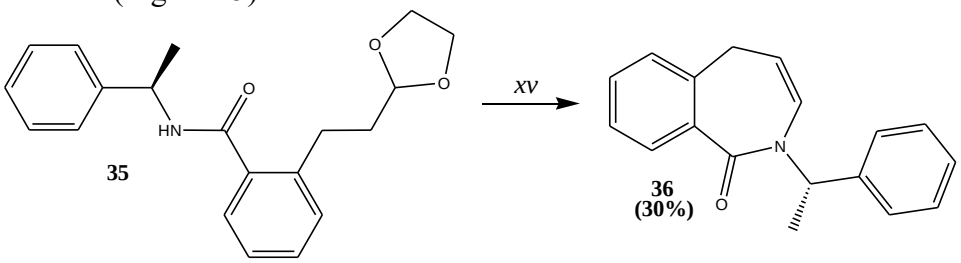


**Figure 15**. Synthesis of a benzazepine derivative (**36**). *Conditions and Reagents*: *xv* = compound **35**, HCl, TosOH, $CHCl_3$, MW 200, 5 min.

Other studies showed the synthesis of compound 1-[(4-Methylphenyl)sulfonyl]-1,2,3,4-tetrahydro-5Hbenzo[b]azepin-5-one from methyl 2-(4-methylphenylsulfonamido)benzoate was via alkylation with ethyl γ-bromobutyrate and followed by an intramolecular cyclization using microwave irradiation (Figure 16).[xxvi]

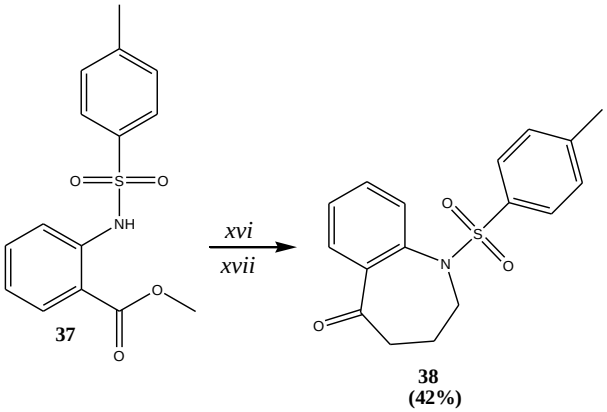


**Figure 16**. Sinthesis of a benzoazepinone analog (**38**). *Conditions and Reagents*: *xvi* = Methyl 2-(4-methylphenylsulfonamido)benzoate (**37**), DMF, NaH, ethyl-4-bromobutanoate 90 °C; *xvii* = EtOH/AcOH/HCl, MV 160 °C, 10 min.

Besides, another study indicated that compound 2-(2-aminophenyl)-1-(2-chlorophenyl)ethanol (**39**) was directly cyclized by an intramolecular Buchwald-Hartwig coupling in the presence of Xantphos and palladium under irradiation conditions to produce a benzoazepine derivative (Figure 17).[xxvii]

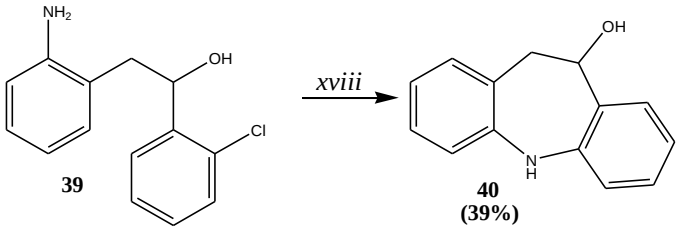


**Figure 17**. Synthesis of 10,11-dihydro-5H-dibenzo[b,f]azepin-10-ol (**40**). *Reagents and Conditions: xviii* = compound (**39**), $Pd(OAc)_2$, $K_2CO_3$, toluene, MW 135 ºC, 8 hs.

Other data showed the deprotection of a biaryl derivative (**41**) upon treatment with TFA/DCM (Figure 18). This reaction involves a biphenyl-carbaldehyde derivative as an intermediary, which reacted with an ethynyl-benzene under microwave irradiation to form 2,3-dimethoxy-6-(4-methoxy-benzyl)-7-phenylethynyl-6,7-dihydro-5H-dibenzo[c,e]azepi- ne.[xxviii]

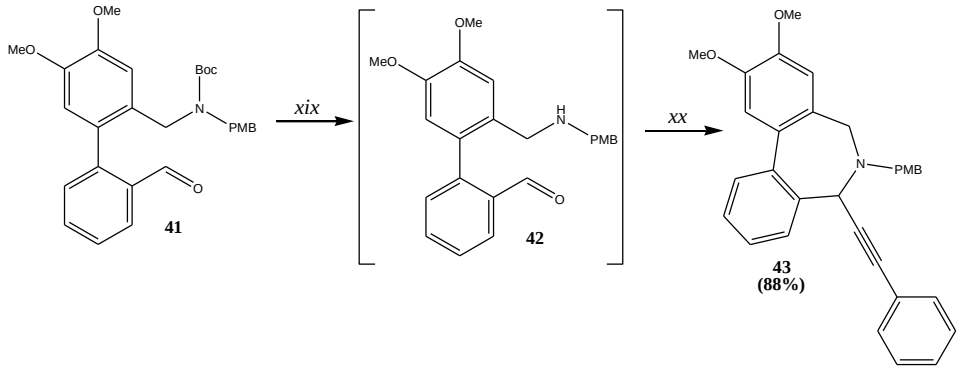


**Figure 18**. Synthesis of dibenzoazepine (**43**). *Conditions and Reagents: xix* = TFA-DCM, 0 ºC, 45 min; *xx* = Ethynyl-benzene, CuBr, 100 ºC MW.

Metha and col. (2011) displayed the microwave-assisted diastereoselective multicomponent reaction (Figure 19) to synthesize the compound 6-tert-butyl-7-oxo-6,7-dihydro-5H-

dibenzo[c,e]azepine-5-carboxylic acid tert-butylamide (**45**) from 2'-formyl-[1,1'-biphenyl] -2-carboxylic acid (**44**).[xxix]

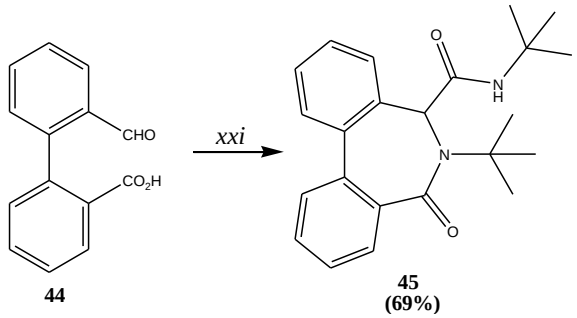


**Figure 19**. Synthesis of Dibenzo[c,e]azepinone (**45**). Conditions and Reagents: *xxi* = compound (**44**), *p*-methoxybenzylamine, tert-butyl isocyanide, $CF_3CH_2OH$, $Na_2SO_4$, MW 110 ºC, 15 min.

Other report indicates the reaction of *N*-allyl-2-amino-**N**-methylbenzamide (**46**) with $NaNO_3$ to form an azide as intermediary followed with an intramolecular cyclization to produce the compound 2,4-dimethyl-3H-benzo[e][1,4]diazepin-5(4H)-one (**47**) under microwave irradiation (Figure 20).[xxx]

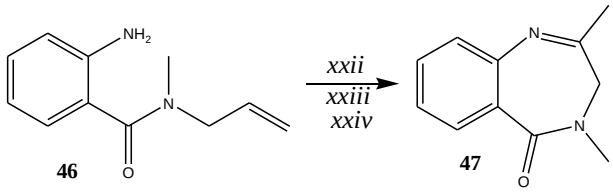


**Figure 20**. Synthesis of a diazepinone derivative (**47**). Conditions and Reagents: *xxii* = compound **46**, HCl, $NaNO_2$, AcOH, 30 min; *xxiii* = $NaN_3$, $Et_2O$, 40 min; *xxiv* = DMF, MW (150), 80 ºC, 5 min.

## CONCLUSIONS

The assisted-microwave method a chemical tool to synthesize several compounds; these reactions can provide high yields and high reaction speeds and can be used for the synthesis and reactions of different benzo- dibenzoazepines derivatives. It is noteworthy that these data can be used to make decisions in the development of new benzo- dibenzoazepines derivatives.

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