A RESEARCH ARTICLE LENTIL UNEXPLORED – DESIGN, SYNTHESIS, DEVELOPMENT AND CHARACTERIZATION OF NEWER SUBSTITUTED DERIVATIVE OF FIVE MEMBER HETEROCYCLIC COMPOUND

Narwate Balaji Malhari[1], Dr. Vijaysinh Uttamrao Sable[1] and Dr. Rakesh Meel[1]

[1] Department of Pharmacy, Sunrise University, alwar, Rajasthan
[*]Email – Balaji.narwate81@gmail.com

ABSTRACT- The combinations of five-membered hetero-aromatic compounds such as pyrazoles, isoxazoles and 1,2,4-oxadiazoles are of interest to the pharmaceutical industry and scientific data for their applications. Although there are many ways to prepare these compounds, new variations are constantly emerging as they provide many recreational and therapeutic benefits.

This article presents a new method for the synthesis of 4-iodopyrazole, pyrazole, isoxazole, 1,2,4-oxadiazole and/or 1,2,4-oxadiazepines. In the first part of this study, electrophilic cyclization of α,β-alkyne hydrazones with molecular iodine and copper iodide was investigated as a new method for the synthesis of 4-iodopyrazoles and pyrazoles. Initially, α,β-alkyne hydrazones were prepared by the reaction of propargyl aldehydes and ketones with hydrazines.

The α,β-alkyne hydrazone was then treated with molecular iodine in the presence of $NaHCO_3$ to give 4-iodopyrazole in good yield. Then, the same reaction with CuI in the presence of %yields the corresponding synthesis pyrazole. In addition, ferrocenyl substituted 4-iodopyrazoles combination and pyrazole derivatives were synthesized from the corresponding α,β alkyne hydrazones substituted using electrophilic cyclization reactions.

In the second part of this study, the reaction between propargyl aldehyde and amidoxime was evaluated. This reaction only produces more compounds.

Keyword: Pyrazole, Isoxazole, 1,2,4-oxadiazole etc.

DOI: 10.48047/ecb/2022.11.10.29

Aim of the study

In this study, we will explore new methods to synthesize biologically important heteroaromatic compounds, including pyrazoles, isoxazoles, 1,2,4-oxadiazoles, and 1,2,4-oxadiazepines. First, we perform electrophilic cyclizations of α,β -alkynehydrazones 186 derived from propargylic aldehydes and ketones 118 and hydrazines 185 to generate the corresponding pyrazoles 187 and 188 regioselectively. Upon treatment with molecular iodine, acetylenic derivatives of hydrazone 186 can undergo electrophilic cyclization to give 4-iodopyrazoles 187. We are particularly interested in the synthesis of 4-iodo-1,3,5-trisubstituted and 4-iodo-1,5-disubstituted pyrazoles as they can play an important role in the formation of biologically active pyrazole derivatives owing to the iodinated products obtained. As mentioned above, iodo-substituted pyrazoles are important precursors for the synthesis of highly substituted pyrazole derivatives via metal--catalyzed cross-coupling reactions.

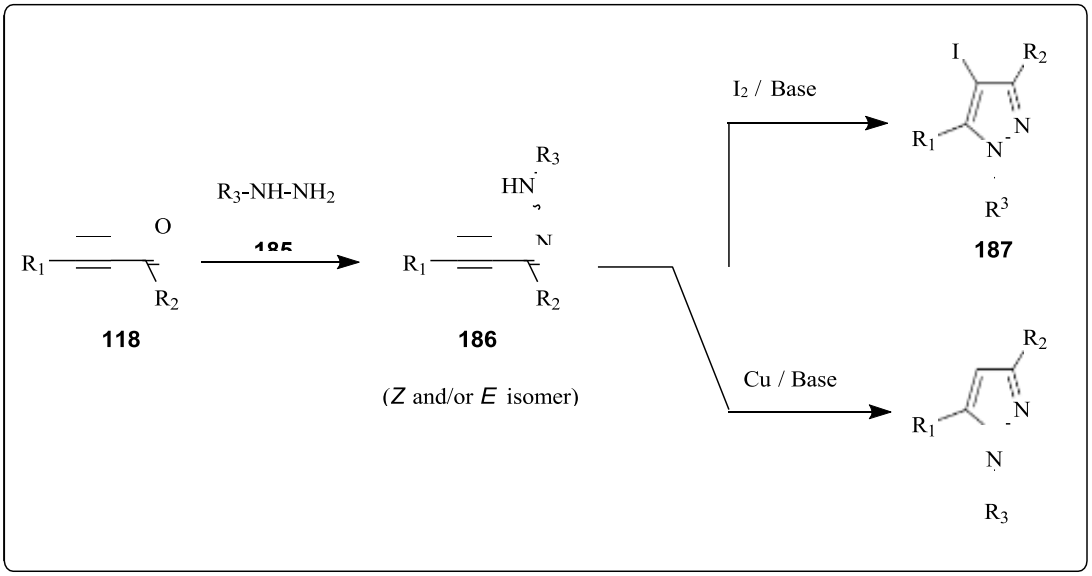


Fig.-1 Synthesis of pyrazoles and 4-iodopyrazoles via electrophilic cyclization.

INTRODUCTION

Heterocyclic compounds are organic compounds which have at least one element other than carbon, such as oxygen, nitrogen or sulfur, within a ring skeleton. Heterocyclic compounds are

not only found in natural products, such as aflatoxin B_1, caffeine, reserpine and biotin [2], but also obtained synthetically. Heterocyclic compounds are generally classified according to the number of atoms on the ring. Some examples for the known heterocyclics include 3-membered oxiranes and aziridines, 4-membered oxetanes and azetidines, 5-membered furans, pyrroles and thiophenes, and 6-membered pyridines [3].

Many alkaloids, vitamins, antibiotics and synthetic medicines as well as dyestuffs are heterocyclic compounds. The seven of the top 10 best selling prescription drugs include heterocyclic moieties in their structures, which emphasizes the importance of heterocyclic compounds for human life [4]. Therefore, the synthesis of heterocyclic compounds has attracted great attention in organic community for a long time because of their biological activities, properties and applications. Pyrazoles, isoxazoles and 1,2,4-oxadiazoles are important classes of heterocyclic chemistry due to the broad range of biological activities they possess, which will be discussed in the following sections.

The synthesis of these ring systems has been shown to involve:

(i) Synthesis of propargylic aldehydes (alkenals) and ketones (alquinones) 118 corresponding alkynes,

(ii) Synthesis of hydrazone-186 derivatives of propargylic aldehydes and ketones,

(iii) I2-mediated electrophilic cyclization of hydrazone derivatives 186 to 4-iodopyrazoles 187

(iv) CuI-mediated electrophilic cyclization of 186 hydrazone derivatives to form 188 pyrazoles

(v) Synthesis of 190 amidoxime derivatives from corresponding nitriles,

(vi) Addition synthesis of conjugates (N'-((-3-oxo-1-aryl/alkylprop-1-en-1-yl)oxy)aryl) 191 and/or 1,2,4-oxadiazepine 193 by reaction of amidoximes 190 with propargylic aldehydes and ketones 118, (vii) addition reaction of the conjugates (N'-(3-oxopropenyloxy)benzimidamide) 191 in an acidic medium,

(viii) addition reaction of conjugates (N'-(3-oxopropenyloxy)benzimidamide) 191 under basic conditions, Finally, the scope, limitations, and mechanisms of the formation of 4-iodopyrazoles 187, pyrazoles 188, isoxazoles 112, 1,2,4-oxadiazoles 192, and oxadiazepines 193 are discussed in detail in this article.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were recorded on a Bruker Spectrospin (400 MHz) spectrometer. Chemical shifts are reported in parts per million (ppm) downfield from an internal TMS (trimethylsilane) reference. Coupling constants (*J*) are reported in hertz (Hz), and spin multiplicities are presented by the following symbols: s (singlet), br s (broad singlet), d (doublet), t (triplet), q (quartet), m (multiplet). DEPT ^{13}C NMR information is given in parentheses as C, CH, CH_2 and CH_3. Band positions are reported in reciprocal centimeters (cm^{-1}). Band intensities are indicated relative to most intense band, and are listed as: br (broad), vs (very strong), s (strong), m (medium), w (weak), vw (very weak). Flash chromatography was performed using thick-walled glass columns and ‘’flash grade’’ silica (Merck 230-400 mesh). Thin layer chromatography (TLC) was performed by using commercially prepared 0.25 mm silica gel plates and visualization was effected with short wavelength UV lamp. The relative proportions of solvents in chromatography solvent mixtures refer to the volume: volume ratio. All commercially available reagents were used directly without purification unless otherwise stated. All the solvents used in reactions distilled for purity. The inert atmosphere was created by slight positive pressure (ca. 0.1 psi) of argon. All glassware was dried in oven prior to use.

General procedure for the preparation of propargyl aldehydes (118)

Corresponding alkyne (50 mmol) was dissolved in dry THF (125 ml) and the solution was cooled to -40 ^{o}C under argon. *n*-Butyllithium (1.65 M in Hexanes, 30.3 ml, 50 mmol) was added dropwise over 2 min maintaining the temperature between - 35 ^{o}C and -40 ^{o}C. After completion of the addition, anhydrous DMF (7.75 ml, 100 mmol) was added in one portion and the cold bath was removed. The reaction mixture was allowed to warm to room temperature and aged for 30 min. THF solution was poured into a vigorously stirred biphasic solution prepared from a 10% aqueous solution of KH_2PO_4 (270 ml, 200 mmol) and diethylether (250 ml) cooled over ice to 5 ^{o}C. Layers were separated and the organic extract was washed with water (2 x 200 mL). Combined organic layers were dried over $MgSO_4$, filtered and concentrated to give the crude propargyl aldehyde which was filtered through a padof silica gel using 9:1 mixtures of hexanes/EtOAc as the eluent [164].

General procedure for the preparation of 4-phenylbut-3-yn-2-one (118g).

To a 100 mL two-necked round-bottomed flask equipped with magnetic stirring under nitrogen at -70 ^{o}C were added the terminal alkyne (10 mmol) and THF (50 mL). The solution was warmed up to 0 ^{o}C, stirred at this temperature for 30 min and then cooled at -70 ^{o}C prior to the addition of a solution of $ZnCl_2$ (1 eq., 1 M solution in THF). The solution was warmed and stirred at room temperature for additional 15 min and then recooled at -70 ^{o}C. Acetyl chloride was added in one portion. The reaction mixture was warmed to room temperature and stirred for additional 40 min, then diluted with hexane (10 mL) and washed with brine (3x10 mL). The organic phase was dried over magnesium sulphate and filtered. The solvents were evaporated and the residue purified by silica gel column chromatography eluting with EtOAc/hexane yielding 1,3-diphenylprop-2-yn-1-one. ^{1}H NMR (400MHz, $CDCl_3$): δ 7.55 (d, J = 8.3 Hz, 2H), 7.43 (t, J = 7.4 Hz, H), 7.36 (m, 2H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 184. 3 (C), 133.0 (CH), 130.7 (CH), 128.6 (CH), 119.9 (C), 90.2 (C), 88.3 (C), 32.6 (CH_3).The spectral data were in agreement with those reported previously for this compound [163, 182].

General procedure for the preparation of 1,3-diphenylprop-2-yn-1-one (118h)

Benzoyl chloride (6 mmol), $PdCl_2(PPh_3)_2$ (0.1 mmol) and Et_3N (6 mmol) in THF (20 ml) were stirred for 10 min under argon atmosphere at room temperature. CuI (0.1 mmol) was added and the reaction mixtue was stirred for another 10 min before adding phenylacetylene (5 mmol). After 6 h at room temperature, THF is removed under reduced pressure and the crude mixture was extracted with ethyl acetate and0.1 N HCl and a saturated NH_4Cl solution. The organic phase was dried over magnesium sulphate and filtered. The solvents were evaporated and the residue purified by silica gel column chromatography eluting with hexane/EtOAC yielding 1,3-diphenylprop-2-yn-1-one (98%).

Synthesis of acetylferrocene (198)

Ferrocene (**180**) (2g, 10.8 mmol) was dissolved in dry CH_2Cl_2 (9 mL) by constant stirring under argon. Then acetyl chloride (0.92ml, 11.8 mmol) was added to the resultant orange/red solution. The flask was immersed in a 0-5 ^{o}C ice-water bath. Anhydrous aluminum chloride (1.44 g, 10.8 mmol) was slowly added in small portions to the reaction

flask. The reaction mixture was stirred at room temperature for 2 h and then it was recooled to 0-5 ^{o}C by a fresh ice-water bath. By the slow addition of cold water (4 x 0.5 ml), the reaction mixture was hydrolyzed. Then a further 3 ml of cold water was added more rapidly. The hydrolyzed reaction mixture was extracted with CH_2Cl_2 and combined organic extracts were washed with 5% NaOH solution followed by brine solution. The organic phase was dried over magnesium sulfate and filtered off. An orange/red solid was obtained after solvent was removed on rotary evaporator. The resultant solid was purified by flash column chromatography on silica gel using 9:1 hexane/ethylacetate as the eluent to give acetylferrocene (**198**) (1.96 g, 80%).

Synthesis of (2-formyl-1-chlorovinyl) ferrocene (44)

In a two necked flask, acetylferrocene (**198**) (2 g, 8.8 mmol) and DMF (2.17 ml, 28.2 mmol) were added under argon. The flask was cooled to 0 ^{o}C by ice-water bath and the brown reaction mixture was stirred for 10 minutes. Separately, in a round-bottom flask, DMF (2.17 ml, 28.2 mmol) was added and cooled to 0 ^{o}C under argon. Then cautiously phosphorus oxychloride (2.21 ml, 28.2 mmol) was added to DMF with good stirring. The resultant viscous red complex was slowly (over 30 minutes) transferred to the two neck flask containing acetylferrocene (**198**) and DMF by a dropping funnel. After the addition was completed, the contents of the flask were stirred at 0 ^{o}C for approximately 2 h until the color of reaction mixture changed from dark brown to olive green and then to dark blue. A 20 ml portion of diethyl ether was added, and the mixture was stirred vigorously. Then with continued cooling with ice- water bath, sodium acetate trihydrate (10.18 g, 74.6 mmol) was carefully added to the reaction flask in one portion followed by addition of water (2 ml). The ice water bath was removed and a color change in organic layer from colorless to ruby red, indicating the formation of formyl derivative, was observed. After 1 h, additional ether (2 ml) was added and the stirring was continued for 3 h at room temperature for complete quenching. The reaction mixture was extracted with diethyl ether. The organic extracts were combined and washed with saturated sodium bicarbonate solution. After dried by magnesium sulfate and filtered, organic phase was concentrated on rotary evaporator, yielding (2-formyl-1-chlorovinyl)ferrocene (**44**) (2.25 g, 93%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.06 (d, 1H, J = 7.1 Hz), 6.38 (d, 1H, J = 7.1 Hz), 4.73 (t, 2H, J = 1.68 Hz), 4.54 (t, 2H, J = 1.68 Hz), 4.22 (s, 5H). The spectral data is in agreement with those

reported previously for this compound [167].

RESULTS

Synthesis of propargyl aldehydes and ketones

Synthesis of propargyl aldehydes

In the first part of the study, propargyl aldehydes **118** were prepared from corresponding terminal alkynes **194** in good to high yields by using a standard literature procedure [62]. Terminal alkynes **194** were first treated with *n*-BuLi in THF at -40 ^{o}C under argon. Then the resulting lithium alkynides **195** were allowed to react with DMF at room temperature for 1 h to afford propargyl aldehydes **118**. Note that a reverse quench into a phosphate buffer has proved to be the key for these high yielding formylation reactions. Proposed mechanism for the formation of propargyl aldehydes **118** is shown in Figure 2.

As depicted in Figure 2, six different derivatives of 3-aryl or alkyl substituted propargyl aldehydes were synthesized, the overall yields of which ranged from 52 to 94%. The best yield was obtained for 4-methoxyphenyl derivative **118c** while the lowest yield was found for thiophen-3-yl derivative **118d**.

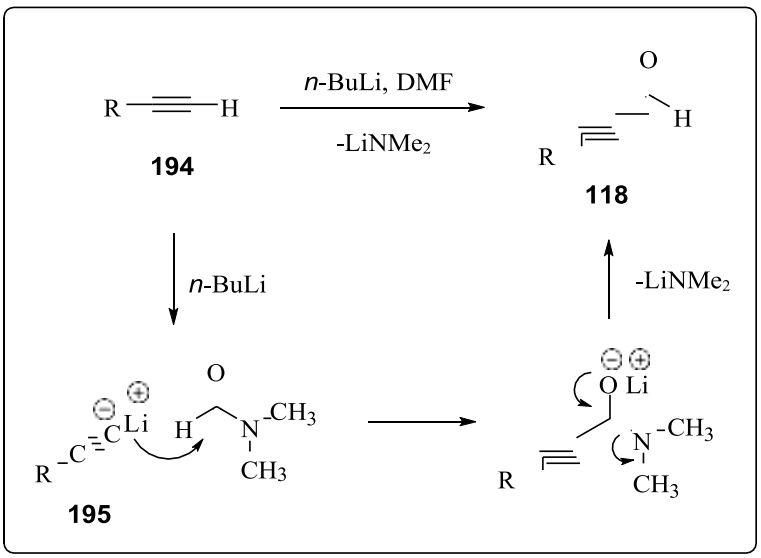


Figure2 . Proposed mechanism for the formation of propargyl aldehydes**.**

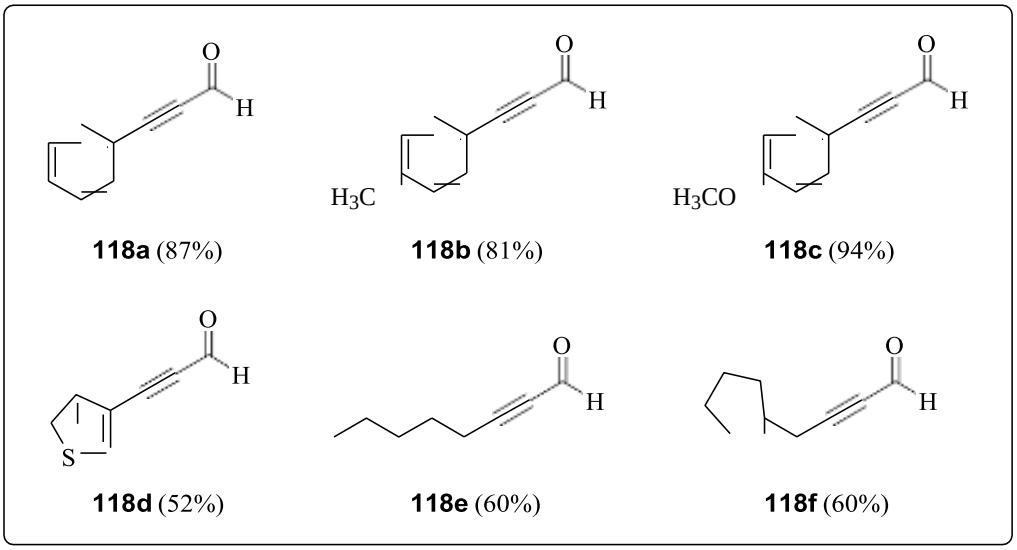


Figure 3. Structures of the synthesized propargyl aldehyde derivatives.

Synthesis of propargyl ketones

4-Phenylbut-3-yn-2-one (**118g**) was prepared from phenylacetylene (**194a**) by using a slightly different procedure (Figure 3) [63]. The treatment of phenylacetylene (**194a**) with *n*-BuLi first yielded in situ lithium phenylacetylide, then the reaction of which with $ZnCl_2$ followed by acetyl chloride addition resulted in the formation of the desired propargyl ketone **118g** in 89% yield.

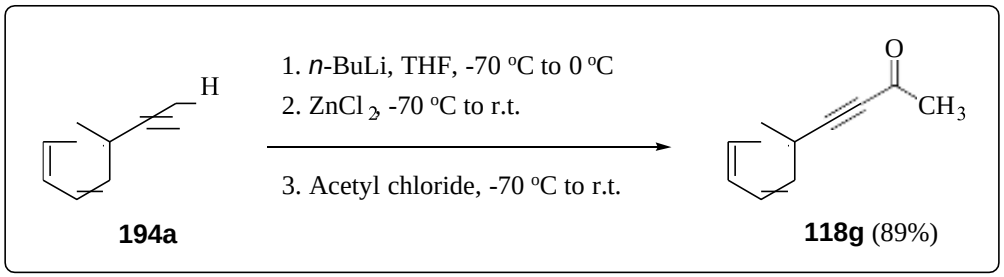


Figure 3. Synthesis of 4-phenylbut-3-yn-2-one (**118g**) from phenylacetylene(**194a**).

On the other hand, 1,3-diphenylprop-2-yn-1-one (**118h**) was prepared by a metal- catalyzed cross-coupling reaction [164]. The palladium-catalyzed Sonogashira coupling of benzoyl chloride (**197**) with phenylacetylene (**194a**) at room temperature easily produced the expected propargyl ketone **118h** in 98% yield (Figure 4).

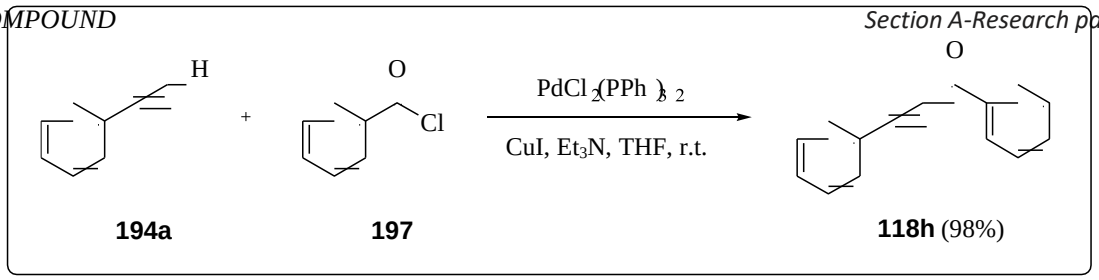


Figure 4. Synthesis of 1,3-diphenylprop-2-yn-1-one (**118h**) from phenylacetylene(**194a**).

Synthesis of 3-ferrocenylpropynal (45)

3-Ferrocenylpropynal (**45**) was synthesized from ferrocene (**180**) as shown in Figure 5. Acetylferrocene (**198**) was first prepared by Friedel-Crafts acylation of ferrocene (**180**) with acetyl chloride in the presence of $AlCl_3$ [165]. Acetylferrocene (**198**) was then treated with Vilsmeier-Haack reagent [166], formed in situ by the reaction between DMF and $POCl_3$, to yield (2-formyl-1-chlorovinyl)ferrocene (**44**) [167]. Subsequently, the reaction of compound **44** with sodium hydroxide in refluxing dioxane afforded ethynylferrocene (**104**) through addition-elimination reaction sequence. Finally, the formylation of ethynylferrocene (**104**) with DMF, according to a known procedure mentioned above [164], produced 3-ferrocenylpropynal (**45**) (Figure 5).

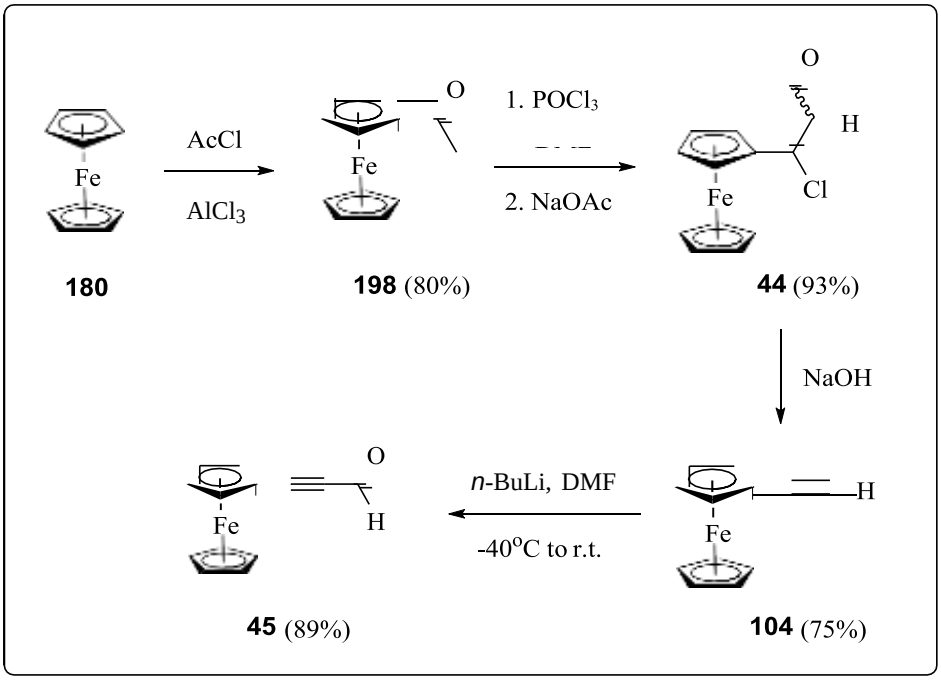
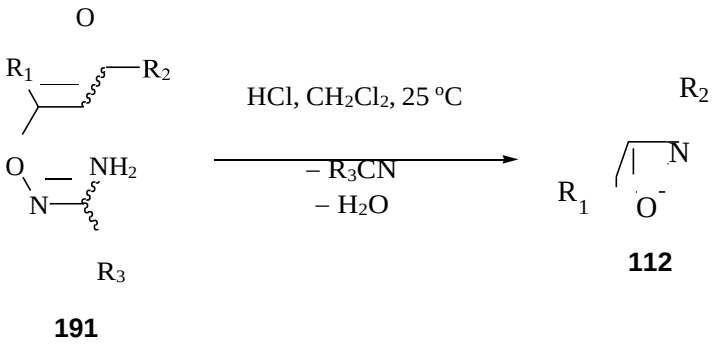


Figure 74. Synthesis of 3-ferrocenylpropynal (**45**).

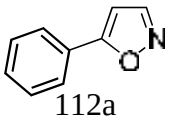
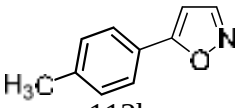
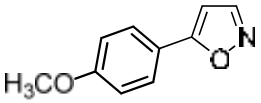
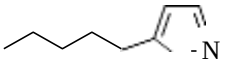
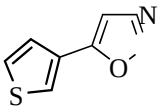
Synthesis of isoxazoles 112 from conjugate addition products 191

For the synthesis of oxadiazepines **193**, the reactions of conjugate addition products **191** were investigated in the presence of hydrochloric acid. Surprisingly, when the conjugate addition products **191** were treated with 2-3 drops of HCl in CH_2Cl_2 at room temperature for approximately 30 minutes, the reactions led to formation of isoxazoles **112** in good yields, without formation of any of the expected oxadiazepines **193**. The results are shown in Table 1. The formation of isoxazoles **112** from conjugated addition products **191** was observed for the first time and quite important from the mechanistic point of view. As seen in Table 1, all conjugated products **191** afforded corresponding isoxazoles **112**. When compound **191a** was employed, acid catalyzed reaction produced 5-phenylisoxazole (**112a**) in 96% yield, which was the highest yield obtained (Table 1, Entry 1). Interestingly, these reactions produced nitrile derivatives (R_3CN) as well, but effort was not spent to isolate them. However, the formation of nitriles in these reactions was proved by HPLC analysis of benzonitrile in the crude reaction mixture obtained in Entry 1 of Table 10. The lowest yield (67%) of isoxazoles was observed for the formation of 5- pentylisoxazole (**112d**) (Table 10, Entry 4). Thiophenyl-substituted isoxazole **112e** was obtained in 87% yield (Table 10, Entry 5). Apparently, the reaction tolerates the presence of aryl, heteroaryl and alkyl functionalities. Interestingly, when treated with acid, conjugate addition product **191l**, which contains a ketone functionality, underwent hydrolysis and afforded 1,3-diketone **209** in 96% yield (Figure 88). An amidoxime derivative, namely benzamidoxime (**190a**), was possibly resulted from this reaction as well, but, in the acidic conditions, it might be converted to salt form which escaped from isolation during column chromatography.

Table 10. Synthesis of isoxazoles.



191 **112**

entry	conjugate addition product	isoxazole	% yield
1	191a	 112a	96
2	191b	 112b	91
3	191c	 112c	78
4	191d	 112d	67
5	191e	 112e	87

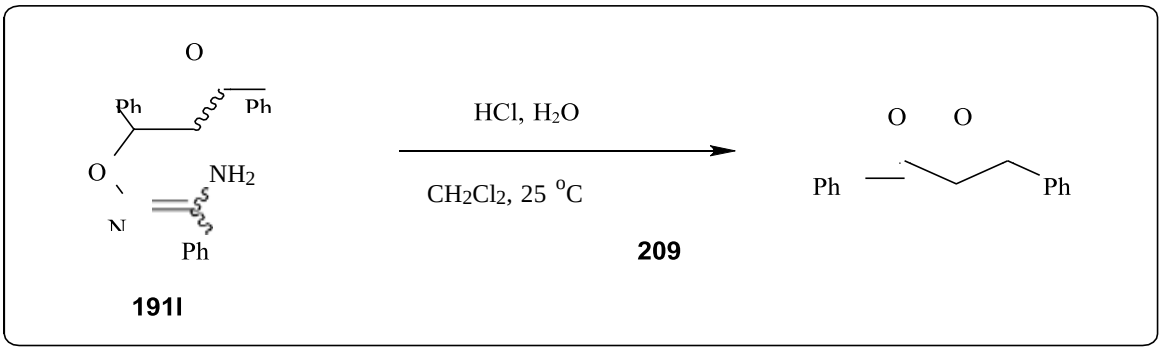


Figure 8. Acid catalyzed hydrolysis of conjugate addition product **191l**.

Conclusion & Summary

Conclusion In summary, we developed a new method for the synthesis of pyrazoles, isoxazoles and 1,2,4-oxadiazoles and 1,2,4-oxadiazepines from propargyl aldehydes and ketones. In the first part of this study, we investigated the electrophilic cyclization of □,□-alkyne hydrazones 186 from propargyl aldehydes and ketones 118 and hydrazine 185. As expected, this reaction leads to the desired pyrazole 188 as a bulk or single product. α,β-alkyne hydrazone 186 allowed molecular iodine in the presence of a base, and the reaction was carried out with CuI in acetonitrile in the presence of base to give pyrazole 188 in good yield. Electrophilic cyclization reactions against various □,□□alkyne hydrazone derivatives186 for the synthesis of 1,5-disubstituted-4-iodo-1H-pyrazoles, 1,3,5-trisubstituted-4-iodo-1H-pyrazole, 1,5- bi- substituted-1H-pyrazole and 1,3,5-tri-substituted-1H-pyrazole.As a result, 23 4-iodopyrazoles and 27 pyrazoles were isolated and characterized. In addition, ferrocenyl substituted pyrazoles were also formed by electrophilic cyclization of the corresponding □,□-alkyne hydrazones. At the end of this study, the reaction between propargyl aldehyde and amidoxime was evaluated. This reaction was found to produce adduct 191 instead of 1,2,4-oxadiazepines 193. Isoxazole 112 was formed in the acidic reaction, and 1,2,4-oxadiazole 192 from compound 191.The reaction mechanism for the formation of heteroaromatics has been proposed. Also, one pot reactions of propargyl aldehydes and amidoximes with bases were used to synthesize 1,2,4-oxadiazoles 192, but this one pot reaction yielded poor results. 3-Aryl-5-ferrocenyl-1,2,4-oxadiazoles, ferrocenylpropanal and amidoxime were produced in a single crucible as they did not form additional compounds. With this new method, 11 new ferrocenyl substituted oxadiazoles were obtained. In summary,

pyrazoles are synthesized by electrophilic cyclization.In particular, pyrazoles will be new initiators for the synthesis of important structures of biological products by coupling reactions using metal catalysts.

In conclusion, synthesis of pyrazoles via electrophilic cyclization reactions were performed successfully. Especially, pyrazoles would be new starting compound for the synthesis of biologically important structures by using metal catalyst coupling reactions.

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