Part –V: Utilities of Active Methylene Compounds and Heterocycles Bearing Active Methyl or having an Active Methine in the Formation of Nitrogenous Heterocycles Having oxygen or sulfur atom

Mohamed Abdel-Megid*1

Chemistry Department, Faculty of Education, Ain-Shams University. Roxy,11711, Cairo, A.R. Egypt

College of science and humanities at Hyrmilla, Shaqra University, KSA
mabdelmegid@yahoo.com, mabdelmegid@su.edu.sa

Abstract
Most of the common and novel synthesized active methylene compounds as well as heterocycles bearing active methyl or having methine site were used in the syntheses of wide variety of five-, six- and seven-membered azaheterocyclic systems having oxygen or sulfur atom in their structures in addition to some oxygenated heterocycles such as pyrans. Many synthetic approaches were used for the preparation of target heterocyclic systems such as cyclocondensation reactions, ring opening-ring closure, cycloaddition, acid-, base-catalyzed reaction, intermolecular cyclization and self-condensation as well as ring–chain tautomerism has been reviewed in this paper.

Keywords: Active methylene, Isoxazles, Thiazoles, Oxadiazoles, Thiadiazoles, Thiazines, Pyrans, Oxazepines, Thiazepines

Introduction
Common and novel synthesized active methylene compounds are useful as a versatile synthetic building block for a variety of functional and pharmacologically active substances. Motivated by this fact and during the last three decades, our work was focused on the use of common and novel synthesized acyclic active methylene compounds as well as heterocycles that having active methyl and methine groups in the formation of some Five-, Six-, and Seven-Memberd azaheterocyclic systems having oxygen or sulfur atom in their structures and evaluated their biological activities.

1. Synthesis of Five-Membered nitrogenous heterocycles with oxygen or sulfur atom

Some important five-membered nitrogenous heterocycles with oxygen or sulfur atom such as isoxazles, thiazoles, oxadiazoles and thiadiazoles as well as thiophene and benzofuran were prepared with the help of the common and novel synthesized acyclic or cyclic active methylene compounds as well as heterocycles having active methyl or methine site in their structures.

1.1. Isoxazole formation

Isoxazole rings are found in some natural products such as ibotenic acid. They also form the basis of drugs including the COX-2 inhibitor valdecoxib, lactamase-resistant antibiotic such as cloxacillin and flucloxacillin. The synthetic androgenic steroid danazol also has an isoxazole ring (Crossley & Browne, 2010). Diverse applications associated with isoxazole moiety led us to develop various synthetic approaches for the formation of them. Most of the newly synthesized isoxazoles afforded through the interaction of hydroxylamine with some prepared compounds, these are:

1.1.1. Acetophenone derivatives

Alkylation of 1,2,4-triazole (1a), imidazole (1b) and benzimidazole (2) with phenacyl bromide (3) led to the formation of three active methylene compounds, 1,2,4-triazolylacetophenone (4a), imidazolylacetophenone (4b) and benzimidazolylacetophenone (5), respectively (Mohamed Abdel-Megid, Elnagdi, & Negm, 2002) (Scheme 1).
Two isomeric isoxazolylazoles were obtained from azolylacetophenones 4 and 5. Thus, when 1,2,4-triazolylacetophenone (4a) condensed with hydroxylamine hydrochloride (6), the oxime 6 was produced, which underwent cyclocondensation reaction on treating with dimethylformamide dimethylacetal (DMFDMA) (8) to afford isoxazolotriazole 9. Whereas its isomeric form 10 was formed via the reaction of the enaminone 9, obtained from condensation of 4a with DMFDMA, with hydroxylamine hydrochloride (Mohamed Abdel-Megid et al., 2002). Similar behavior on benzimidazolylacetophenone (5) took place and the two isomeric isoxazolylbenzimidazoles (13) and (15) were obtained (Scheme 2).

Interestingly, it has been found that the C-2 of chromone is an active site with methine and when it attached by a nitrogenous nucleophile such as hydroxyl amine ring-opening of the r-pyron followed by ring closure reaction took place giving rise to the target isoxazole. Thus, Knoevenagel condensation of 3-formylchromone (16) with thiazolidine-2,4-dione (17) furnished 3-chromenyl- methylidenethiazolidinedione 18, which reacted with an equimolar amount of hydroxylamine hydrochloride (6) in ethanolic sodium hydroxide solution to yield 4-
isoxazolylmethyldene-thiazolidinedione 19 (Ibrahim, Abdel-Hamed, & El-Gohary, 2011). Also, when 2-(6-methyl-4-oxochromeny-3-y1)methyldeneamino-4,5-diphenylfuran-3-carbonitrile (22), obtained from the condensation of 2-aminofurancarbonitrile (20) with 6-methyl-3-formylchromone (21), was allowed to react with hydroxylamine hydrochloride (6) in boiling pyridine–water mixture, a nitrogen bridge-head triheterocyclic system having isoxazole ring in its structure 23 was produced by the same manner explained for the compound having chromone nucleus (M. Abdel-Megid, Elkazak, Seada, & Farouk, 2010). (Scheme 29).

Scheme 3: Formation of substituted and fused isoxazoles

The addition of hydroxyl amine to the enone 25, which formed by condensation of 3-formylchromone (16) with 3-acetylquinolone (24) depend on reaction medium and molar ratio. When compound 25 was subjected to react with equimolar amount of hydroxylamine hydrochloride (6) in boiling DMF-ethanol mixture, the isoxazolyl derivative 26 was produced but when the reaction was carried out in glacial acetic acid it proceeds in a completely different manner and isoxazolyquinolone 27 was obtained. The reaction of both 26 and 27 with hydroxylamine hydrochloride in boiling pyridine gave the bisoxazolylquinolone 28 which could be also obtained by reaction of compound 25 with excess with hydroxylamine (1:2 ratio) hydrochloride in boiling pyridine (Abass, Abdel-Megid, & Hassan, 2007) (Scheme 4).

Scheme 4: Formation of bi-isoxazolyl quinolinones

Moreover, treatment the enone 25 with hydrazine hydrate in glacial acetic acid followed by addition of hydroxylamine hydrochloride in dry pyridine afforded pyrazolylisoxazolylquinoline none 29, which can be also obtained on addition of hydrazine hydrate to 26 in glacial acetic acid (Abass et al., 2007) (Scheme 5).
Addition of thiourea (30), cyanothioacetamide (31) and 2-thiobarbituric acid (32) to α, β-unsaturated carbonyl center of compound 25 in boiling ethanol containing piperidinium acetate yielded, pyrimidinethione 33, thioxopyridinecarbonitrile 34 and pyranopyrimidinethione 35, respectively. Isoxazoles carrying pyrimidinethione 36, pyridinecarbonitrile 37 and pyranopyrimidinethione 38 were produced when hydroxylamine hydrochloride (6) reacted with 33, 34 and 35, respectively (Abass et al., 2007) (Scheme 6).

Scheme 5 Formation of pyrazolylisoxazolyl quinolinone

1.1.3. Synthesized enone does not have chromone

A novel diheterocyclic enone 41 was synthesized from the condensation of 4-acetylpyridazinone 39 with 3-formylquinoline 40 was prepared and used as starting material for the synthesis isoxazole and other heterocyclic systems. Thus, pyridizylquinolylnylisoxazole 42 obtained by treating the enone 41 with hydroxylamine hydrochloride (6) (M. Abdel-Megid, 2006) (Scheme 7).

On the other hand, when p-phenylenediamine (43) was subjected to react with both phenyl isothiocyanate (44a) and p-chlorobenzoyl isothiocyanate (44b), the respective p-bismuthioduro derivatives 45a, b was formed. Treatment of 45a, b with ethyl chloroacetate (46) afforded the bis-thiazolidinone 47a, b. Condensation of 47a with m-nitrobenzaldehyde (48) yielded the cyclic enone 49. The action of hydroxylamine hydrochloride upon 49 gave p-bis(isoxazolothiazolidine) phenylenes (50) (M. Abdel-Megid & M.A.A. Awas, 2002) (Scheme 8).
Moreover, cyclocondensation of hydroxylamine hydrochloride (6) with 5-Arylidene-2-phenyliminothiazolidinone 51, in boiling ethanol (Gabr, Abdel-Megid, Awas, & Abdel-Fatah, 2010) afforded thiazoloisoxazole derivative 52 (Scheme 9).

1.1.4. Ethyl cyanoacetate derivative

Treatment of chloropyrimidinecarbonitrile 53 with ethyl cyanoacetate 54 afforded the ethyl cyanoacetate derivative 55. The action of hydroxylamine hydrochloride upon 55 in refluxing ethanol led to the formation of the oxime 56, which underwent ring closure on heating with sodium ethoxide to give pyrimidopyridoisoxazole 57 (M. Abdel-Megid, 1995) (Scheme 34).
1.2. Thiazole formation

Recently, various synthetic strategies for thiazolidinone derivatives as well as their biological significance were summarized in a review (Kaur Manjal et al., 2017). The 1,3-thiazolidin-4-ones possess wide range of pharmacological activities such as anti-cancer, anti-diabetic, anti-microbial, anti-viral, anti-inflammatory (Lakhan & Singh, 1991) and anti-convulsant. In view of the varied physiological activities of thiazolidiones (el-Feky & Abd el-Samii, 1995), it was of interest to synthesized thiazole derivatives of a potential biological activities using active methylene compound such as thioglycollic acid (58), haloacetic acid or its ethyl ester (46) and phenacyl bromide (3).

1.2.1. Thioglycollic acid

Thioglycollic acid (58) is often called mercaptoacetic acid. It contains both a thiol (mercaptan) and carboxylic acid functional groups in addition to active methylene center. Cycloaddition of thioglycollic acid to C=N of arylideneamino group afforded the target thiazolidine. Thus, condensation of 4-aminopyrimidinecarbonitrile (59) with 1-formyl-2-naphthol (60) yielded 4-arylideneaminopyriminethione 61, which submitted to react with thioglycollic acid (58) to afford thioxopyridinylthazolidinone 62 (M. Abdel-Megid, Abdel-Rahman, & Ali, 1998). Also, condensation of p-phenylenediamine (43) with some aromatic aldehydes furnished the respective p-bis(arylidineamino)phenylenes 63a-c, which underwent cycloaddition with thioglycollic acid in dry solvent to give p-bis(aryltiazol- idiny1)phenylenes 64 a-c, respectively (M. Abdel-Megid & M.A.A. Awas, 2002). The action of thioglycollic acid (58) in dry dioxane upon p-chlorobenzylideneanisofuran 67, which obtained from the condensation of 2-amino- furancarbonitrile 20 with p-chlorobenzaldehyde 65 not gave the target thiazolidinone 67 but compound 68 was obtained (M. Abdel-Megid, Elkazak, et al., 2010) (Scheme 11).

![Scheme 10: Formation of isoxazolopyridopyrimidine](image-url)
Furthermore, the same action was observed in case of arylidene hydrazide or arylidene carbohydrazide. Therefore, 2-hydrazinopyrimidine 69 with 3-formylindole (70) gave the hydrazone 71, which on reacting with thioglycollic acid (58) in dioxane yielded indolythiazol- idinylaminopyrimidine 72 (M. Abdel-Megid, Awas, Seada, Elmhdhy, & Elsayed, 2010). Also, cycloaddition of thioglycollic acid (58) on arylidene- carbohydrazides 74a, b obtained from condensation of 73 with aromatic aldehydes afforded the corresponding thiazolidenone derivatives 75a, b (M. Seada, Fawzy, Jahine, Abd El-Megid, & Saad, 1989) (scheme 12).

Scheme 12: Thiazolidinone formation

Synthesized active methylene compound namely, pyridazinyl-butane-1,3-dione 77 was obtained from the reaction of 4-acetylpyridazinone 39 with ethyl acetate (76) under casein condensation (M. Abdel-Megid, Gabr, Awas, & Abdel-Fatah, 2009). Reaction of compound 77 with acetoephonethiosemicarbazone 80 prepared by the condensation of p-nitroacetophenone (78) with thiosemicarbazide (79) afforded thioxopyrimidinylpyridazinone 81. Addition of thioglycollic acid (58) to 81 in dry benzene cyclocondensation took place giving rise to thiazolidinylpyrimidinylpyridazinone 82 (M. Abdel-Megid et al., 2009) (Scheme 13).

Scheme 13: Formation of thiazolidinylpyrimidinylpyridazinone

1.2.2. Haloacetic acid and its ethyl ester.

Addition of isothiocyanate to amines or to active methylene center afforded thiourea derivatives, which underwent cyclocondensation with haloacetic acid and its ethyl ester to yield the target thiazolidinones. Thus, addition of phenyl isothiocyanate (44a) to hydrazine hydrate, o-phenylene- diamine (83) and 2,6-diaminopyridine (84) afforded bis(N-phenyl) thiourea (85), 1,2-bis(N-phenylthioureido) benzene (86) and 2,6-
bis(N-phenylthioureido) pyridine (87), respectively (Seada M., Abdel-Rahman M. R., & Abdel-Megid M., 1993). When the monochloroacetic acid (88) was allowed to react with bis(N-phenyl) thioureas 85-87, the corresponding bis thiazolidinone derivatives 89-91 were obtained (M. Seada et al., 1989) (scheme 38).

Scheme 14: Formation of bis-thiazolidinones

Moreover, the tetra-thiazolidinones 94 and 95 were formed via the action of phenyl isothiocyanate (44a) upon 47a, b in the presence of DMF-KOH mixture followed by addition of ethyl chloroacetate (46). The formation of both 94 and 95 probably formed through the non-isolable intermediates 92 and 93 respectively (M. Abdel-Megid & M.A.A. Awas, 2002) (Scheme 15).
Also, alkylation of sulfanylquinoline derivative 96 with ethyl chloroacetate (46) furnished ethyl quinolinylthioacetate 97, which reacted with o-aminothiophenol (98) to furnish benzothiazolymethylthioquinoline (99) (Ismail, Abdel-Megid, & Hassa, 2004) (Scheme 16).

Scheme 16: Formation of benzothiazole derivative

1.2.3. Phenacyl bromide

Hydrazonolysis of 3-chloropyridazinecarbonitrile 100 with hydrazine hydrate afforded 3-amino- pyrazolopyridazine 101. Addition of phenyl isothiocyanate (58) to 101 yielded 1,3-disubstituted thiourea (102), which converted to diphenylthiazole derivative 103 by the action of phenacyl bromide (3) (M. Seada et al., 1989) (Scheme 17).

Scheme 17: Formation of diphenylthiazole derivative

1.2.4. Formation of thiazolopyrimidine and related compounds

A series of thiazolopyrimidine derivatives was designed and synthesized in our lab. Thus, the action of N-phenylthiourea (104) and guanidine hydrochloride (105) upon 5-arylidene-thiazolidinone 51 in boiling dimethyl formamide furnished thiazoloprimidinethione 106 and aminothiazolopyrimidine 107 (M. Seada, Abdel-Megid, & El-Deen, 1993) (Scheme 18).

Scheme 18: Formation of thiazolopyrimidines
Similarly, the cyclic enones 49a, b reacted with N-phenylthiourea (104) and acetamidine hydrochloride (108) in DMF to afford the respective bis (pyrimidothiazolin3-yl) phenylenes 109a, b and 110 a, b (M. Abdel-Megid & M.A.A. Awas, 2002) (Scheme 19).

![Scheme 19: Formation of bis (pyrimidothiazolin3-yl) phenylenes](image)

Furthermore, alkylation of 2-sulfanylpyrimidinocarbonitrile (111) with chloroacetic acid (88) produced 2-carboxymethylthiopurimidine (112). Boiling of 112 in acetic anhydride, sodium acetate and glacial acetic acid mixture afforded the thiazolopyrimidine (113), whereas its isomeric form 115 was obtained on reacting 111 with chloroacetyl chloride (114) (M. H. Abdel-Megid, Awas, Seada, El-Mahdy, & Elsayed, 2009) (Scheme 20).

![Scheme 20: Formation of thiazolopyrimidines](image)

Furthermore, alkylation of 111 with chloroacetonitrile (116) and dioxalyl chloride (117) afforded 3-aminothiazolopyrimidine 118 and trioxothiazolopyrimidine 119, respectively. Treatment of 111 with benzaldehyde and monochloroacetic acid (88) yielded 2-benzylidenethiazolopyrimidine 120. Action of phenyl hydrazine, malononitrile and thiourea upon 120 furnished pyrazolo-thiazolopyrimidine 121, pyranothiazolopyrimidine 122 and pyrimidothiazolopyrimidine 123 (M. H. Abdel-Megid et al., 2009) (Scheme 21).
Scheme 21: Formation of thiazolopyrimidinecarbonitrile derivatives

Also, alkylation of compound 111 with ethyl chloroacetate (46) then reaction the product (124) with DMFDMA (8) afforded the enamino 125, which subjected to react with 2-aminobenzothiazole (126) in boiling acetic acid to give diheterocyclythioether 127 having benzothiazolopyrimidine in its structure (M. H. Abdel-Megid et al., 2009) (Scheme 22).

Scheme 22: Formation of benzothiazolopyrimidine

On the other hand, condensation of 2-indinone (127) with DMFDMA (8) and treatment the product with phosphorous oxychloride afforded 2-chlorindole derivative 128, which converted into indolothiazolopyrimidine (130) when it reacted with 2-aminothiazole (129). The action of 2-aminobenzothiazole (125) upon 128 was studied and giving rise to polyfused thiazolopyrimidine derivative 131 (M. Abdel-Megid, 2006) (Scheme 23).
1.3. Formation of thiophene

Thiophenes are classically prepared by the reaction of 1,4-diketones, diesters, or dicarboxylates with sulfidizing reagents such as P₄S₁₀ such as in the Paal-Knorr thiophene synthesis. Specialized thiophenes can be synthesized similarly using Lawesson's reagent as the sulfidizing agent, or via the Gewald reaction, which involves the condensation of two esters in the presence of elemental sulfur (Joule & Mills, 2013). A new method was used in our work when azolylacetophenones 4a, b reacted with phenyl isothiocyanate (44) to afford in situ an adduct (132) that could not be isolated in pure form. However, when it treated with phenacyl bromide (3), the azolylthiophene derivatives 133a, b was obtained (M. Abdel-Megid, 2003) (Scheme 24).

1.4. Benzofuran formation

Benzofuran and its derivatives are widely used for industrial purposes and also exhibit a broad range of biological activities. A recent review compiles examples synthetic methodologies used for the preparation of benzofurans are described (Kishor, 2017) but did not include the novel method that was done in our laboratory, where benzofuran derivative 136 synthesized by treatment of 1,4-benzoquinone (135) with the enaminone 134, obtained on condensation of acetylpyridazine (39) with DMFDMA (8) in glacial acetic acid (M. Abdel-Megid, 2007) (Scheme 25).

1.5. Formation of oxadiazoles
1,3,4-oxadiazole and its isomers are all known and appear in variety of pharmaceutical drugs including raltegravir, butalamine, fasiplon, oxolamine, and pleconaril (Joule & Mills, 2013). This facts encourage us to prepare them in our laboratory. Therefore, hydrazonolysis of 4-carbethoxypyridazinone 137 with hydrazine hydrate afforded 4-carboxyhydrazidepyridazinone 138, which on condensation with aromatic aldehydes gave the corresponding arylidenehyrazides 139a-c. Compound 139 underwent ring closure on refluxing it in acetic anhydride yielding the respective 1,3,4-oxadiazoles 140a-c (M. Seada et al., 1989) (Scheme 26).

**Scheme 26: Intramolecular cyclization of arylidenehyrazides**

Similarly, condensation of acetohydrazide 141 with aromatic aldehydes gave the respective arylidenehyrazides 142a, b in which the side chain underwent intramolecular cyclization on refluxing with acetic anhydride yielding the corresponding 1,3,4-oxadiazoles 143a, b (M. Abdel-Megid, 1997) (Scheme 27).

**Scheme 27: Formation of oxadiazolylpyrimidines**

On the other hand, alkylation of 2-sulfanylquinoline (144) with ethyl chloroacetate (46) then reaction the product with hydrazine hydrate afforded the acid hydrazide (145). Refluxing of 145 with carbon disulfide in alcoholic potassium hydroxide solution yielded 1,3,4-oxadizole derivative 147 was produced. The formation of 147 may be formed as a product of cyclization of the non-separated intermediate 146 (Ismail et al., 2004) (Scheme 28).
1.6. Formation of 1,3,4-thiadizoles

Treatment of 145 with phenyl isothiocyanate yielded the thiosemicarbazide derivative 148, which on refluxing in poly phosphoric acid (PPA) intramolecular cyclization took place forming 1,3,4-thiadiazole derivative 149 (Ismail et al., 2004) (Scheme 29).

![Scheme 29: Formation of 1,3,4-thiadiazole]

2. Synthesis of Six-Membered heterocycles

Thiazine is one of the most important six-membered nitrogenous heterocycles with sulfur atom and pyran is an oxygenated heterocyclic compounds. Both of them could be prepared using common and novel synthesized acyclic or cyclic active methylene compounds as well as heterocycles having active methyl or methine site in their structures.

2.1. Formation of 1,3-thiazines

Extensive studies have been performed on the synthesis and reactivity of 1,3-thiazines and their benzo derivatives (Weinreb & Orr, 2008). We have been found that most of the synthesized 1,3-thiazines in our laboratory arise from the interaction between thiourea with acyclic and cyclic enones in acid medium. Thus, the action of thiourea upon biheterocyclic enones 151 obtained by condensation of acetylpyridazine 39 with 6-chloro-3-formylchromone (150) afforded 4,6-diheterocyclyl-1,3-thiazines 152. Similarly, treatment the enone 41 with thiourea and N-phenylthiourea yielded 1,3-thiazine derivative 153a, b, respectively (Gabr et al., 2010) (Scheme 30).

![Scheme 30: Formation of 4,6-diheterocyclyl-1,3-thiazines]

By the same manner, the cyclic enones 51 and 49a, b reacted with N-phenylthiourea in ethanol containing few drops of hydrochloric acid yielded the respective thiazolothiazine derivatives 154 and 155a, b (M. Abdel-Megid & M.A.A. Awas, 2002)[7,17] (Scheme 31).
2.2. Pyran Formation

Pyran derivatives are widely found in nature, α-pyrene and γ-pyrene mainly exist in plants. Benzopyran (chromene), chromone, coumarin, flavonoid, isoflavone and anthocyanin can be regarded as pyran derivatives. Among the stable members of this family is tetrahydropyran, sugars often occur in pyranose forms containing the tetrahydropyran ring (Brimble, Gibson, & Sperry, 2008). In our work, we used the enones and enaminones for the preparation either substituted or fused pyran derivatives.

2.2.1. Formation of substituted pyrans.

In cyanooethylation of the azolylacetophenones 4a, b with acrylonitrile (156) in pyridine-water mixture the product obtained did not show CN absorption band in IR spectra. This means that cyanooethylation took place giving intermediate 157, which on intramolecular cycloaddition gave 3-azolylpyrans 158a, b (M. Abdel-Megid, 2003) (Scheme 32).

![Scheme 32: Formation of azolylpyrans](image)

Treatment of the enaminone 134 with hippuric acid (159) in refluxing acetic anhydride yielded the pyrone derivative 160 (M. Abdel-Megid, 2007) (Scheme 33).

![Scheme 33: Formation of pyridazinlpiron](image)

Also, boiling of aceturic acid 162 and hippuric acid (159) in acetic anhydride with the enaminone 161, obtained by condensation of acetylquinolone 24 with DMFDMA (8) furnished pyranyl-quinolinone 164a, b, respectively through the non-separable intermediate 163(Abass et al., 2007) (Scheme 34).
The biheterocyclic enone 165 performed by condensation of formyl derivative 164 with 4-acetyl-pyridazinone 39, was subjected to react with malononitrile (166) in boiling pyridine afforded 4,6-disubstituted aminopyrancarbonitrile 167 (El-mahdy, El-Kazak, Abdel-Megid, Seada, & Farouk, 2009)(Scheme 35).

Also, when the biheterocyclic enone 151 refluxed with acetyl acetone (168) in ethanol containing few drops of piperidine yielded the pyridazinylpyran 169, where the reaction proceeds via nucleophilic carbanion attack at β-position of the α, β-unsaturated center followed by cyclocondensation (Gabr et al., 2010) (Scheme 36).

Nucleophilic attack by carbanion of cyclic active methylene compounds at active methine site of γ-pyran nucleus, ring opening–ring closure reactions took place producing the target condensed pyran. Therefore, refluxing of the enone 18 with 1-phenylpyrazolidine (170), 5,5-dimethyl-cyclohexane-1,3-dione (171) and barbituric acid (172) in boiling sodium ethoxide afforded pyrazolopyran 163, 5-(chromenylmethylidene)thiazolidinone 174 and pyranopyrimidine derivative 175, respectively (Ibrahim et al., 2011) (Scheme 37).
Scheme 37: Formation of some condensed pyrans

Also, condensation of acetylpyridazine 39 with isatin (176) yielded the enone 177. The effect of 5,5-dimethylcycohexane-1,3-dione (171) upon the enones 177 in boiling ethanol containing catalytic amount of triethyl amine giving rise to spiro chromenylindole derivative 177 (Gabr et al., 2010), similarly, diheterocyclyl chromene 178 was prepared by the action of compound 171 upon the enone 151 under the same reaction conditions (Scheme 38).

Scheme 38: Formation of tetrahydrochromene

Furthermore, the condensation of indonone 127 with DMFDMA (8) afforded the enaminone (180). Reaction of compound 180 with N-acetyl and N-benzoyl glycine 181a, b in boiling acetic anhydride, acetamidopyran-2-one 182a and benzamidopyran-2-one 182b were obtained, respectively. Also, compound 180 reacted with some active methylene compounds namely, ethyl cyanoacetate, malononitrile and cyanoacetamide in acetic acid to yield pyranoindol derivatives 183a-c. In addition, fusion of 183a with formamide gave pyrimidopyranoindole 184 (M. H. Abdel-Megid et al., 2009) Scheme 39.
Pyranothiazolopyrimidinone 122 could be also obtained by treatment of 111 with α-cyano cinnamonic (185), the condensed product of malononitrile with benzaldehyde (M. Seada et al., 1993) (Scheme 40).

On the other hand, condensation of acetylquinolone 24 with DMFDMA (8) furnished the enaminone 186. Heating the enaminone 186 in glacial acetic acid, intramolecular cyclization took place giving rise to pyranooquinolinone derivative 187 whereas, treatment of 186 with active methylene compounds such as ethyl cyanoacetate (54) and malonomitrile (166) in basic medium afforded the pyranooquinolinone 188 a, b, respectively (Abass et al., 2007) (Scheme 41).

Moreover, condensation of acetylquinolinone 24 with hydrazine hydrate and phenylhydrazine afforded the respective hydrazones 189a, b, which subjected to react with Vilsmeier-Haack reagent (POCl₃-DMF) to give the
formylpyrazoles 190 a, b. Condensation of formylpyrazole 190b with hydroxylamine hydrochloride in glacial acetic acid did not give the expected oxime or the intermediate carbonitrile 191, in which the hydroxyl group was added to CN forming iminopyranoquinolone, which in turn hydrolyzed to produce pyrazolopyranoquinolinone 192 (Abass et al., 2007) (Scheme 42).

Furthermore, when pyridazinyl-butan-1,3-dione (77) treated with concentrated sulfuric acid, ring closure took place giving rise to pyranopyridazinone derivative 193. The presence of methyl group at position -7 was deduced from its ability to condense with benzaldehyde yielding styrylpyranopyridazine 194 (M. Abdel-Megid et al., 2009) (Scheme 43).

3. Synthesis of Seven-Membered heterocycles

3.1. Formation of thiazepines and oxazepines

Benzodiazepines resulted in the synthesis of heterocycle-fused diazepine derivatives with potential pharmacological activity. Pyridoazepines are recognized to be active in the central nervous system and have a comparable activity to the well-known benzodiazepines. This makes the synthesis and the study of pyridodiazepines, pyridoaxazepines and pyridothiazepines an important research topic (Muylaert, Jatczak, Mangelinckx, & Stevens, 2016). Although these structures have a great similarity with benzodiazepines (M. Abdel-Megid, Abass, & Hassan, 2007), thus, the action of o-aminophenol (195) and o-aminothiophenol (196) upon the enone 41 afforded the corresponding benzoxazepine 197 and benzothiazepine 198 (M. Abdel-Megid & Ismail, 2002) (Scheme 44).
Conclusion

In this study effort to optimize the synthetic procedures for the preparation of various bioactive heterocycles. Herein, we explain how active acyclic and cyclic methylene compounds as well as heterocyclic having active methyl or methine sites were used to synthesize wide varieties of heterocyclic systems by choosing certain starting materials and different synthesizing reagents. This study will help researchers in the fields of organic and medicinal chemistry to design and implement new procedures for the constructions of novel biological components.

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