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β-diketones: Important Intermediates for Drug Synthesis

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Abstract

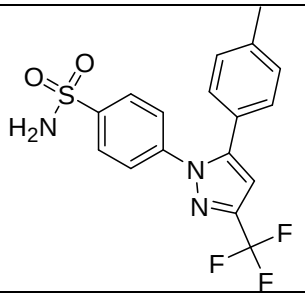
β-diketones or 1,3-diketones are important intermediates not only as a key building blocks for the synthesis of core heterocycles such as pyrazole, isoxazole, and triazole in medicinal chemistry, but also as an invaluable chelating ligand for various lanthanide and transition metals in material chemistry. Apart from the process for the preparation of aromatic beta-diketones by the reaction of an acetophenone and a molar excess of an alphatic ester or an ester of benzoic acid in the presence of sodium alkoxide condensation agent (Claisen condensation) in an aromatic hydrocarbon solvent, various other methods have also been reported by the researchers which are least known and practiced. This review presents an extract of different procedures for synthesis of 1, 3-Diketones described by various authors along with the synthesis of 1, 4-diketones as well as novel β-triketones which may help a researcher to find new possibilities in the related area.

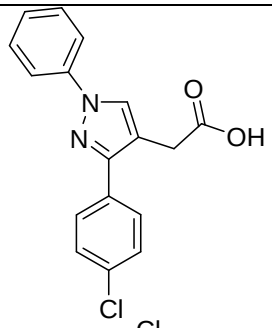
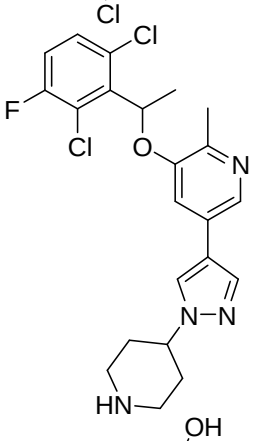
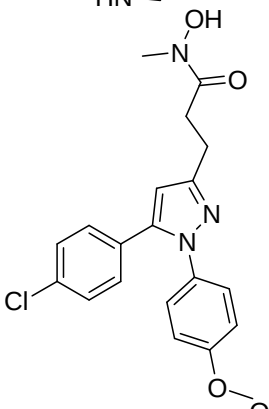
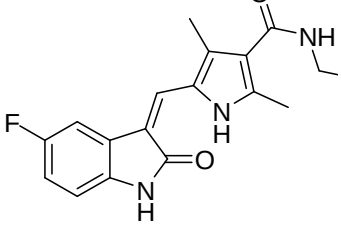
Key words: *β- diketones, β- triketones, 1, 4-diketones, Drug synthesis, Heterocycles.*

Introduction

1, 3-Diketones are one of the most synthetically important classes of compounds. Various drugs containing the heterocyclic moieties, such as pyrazole, isoxazole, carbazole, imidazole and thaizole etc. are the proven drugs against various ailments and are synthesized via a diketone intermediate (Table 1). Also, researchers have found various new compounds containing heterocycles; specially pyrazole, so biologically active as could be considered as promising ligands for future drugs (Table 2).

Table 1: List of important drugs containing the heterocyclic moieties synthesized via β- diketone intermediates (Penning TD *et al*., (1997); Murray WV, Hadden SK, (1992); Baumann M , Baxendale IR, (2011)).

S. No.	Name of the drug	IUPAC name	Structure	heterocyclic moiety	Medicinal use
1.	Celecoxib	4-[5-(4-methylphenyl)-3-(trifluoromethyl) pyrazol-1- yl]benzenesulfonamide		Pyrazole	non-steroidal anti-inflammatory drug

2.	Lonazolac	[3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl]acetic acid		Pyrazole	non-steroidal anti-inflammatory drug
3.	Crizotinib	3-[(1R)-1-(2,6-dichloro-3-fluorophenyl)ethoxy]-5-(1- piperidin-4-ylpyrazol-4- yl)pyridin-2-amine		Pyrazole	anti-cancer
4.	Tepoxalin	3-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)pyrazol-3- yl]-N-hydroxy-N-methylpropanamide		Pyrazole	non-steroidal anti-inflammatory drug
5.	Sunitinib	*N*-(2-diethylaminoethyl)-5-[(*Z*)-(5-fluoro-2-oxo-1H-indol-3-ylidene)methyl]-2,4-dimethyl-1*H*-pyrrole-3-carboxamide		Pyrrole	For the treatment of both renal cell carcinoma and gastrointestinal stromal tumors

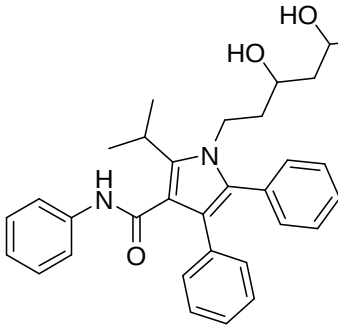
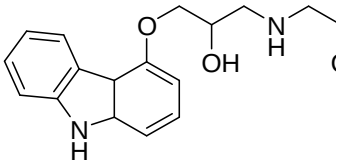
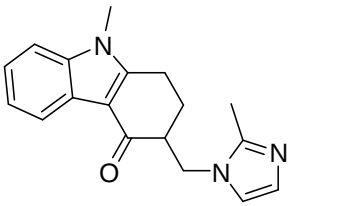
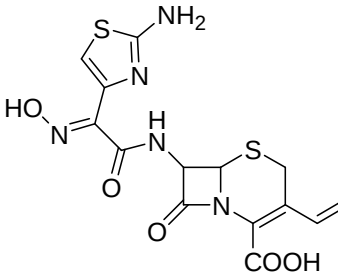
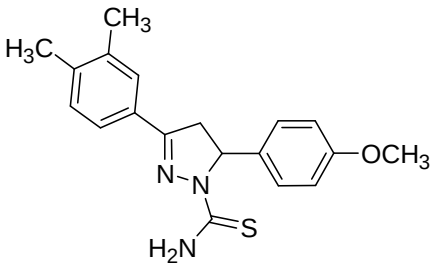
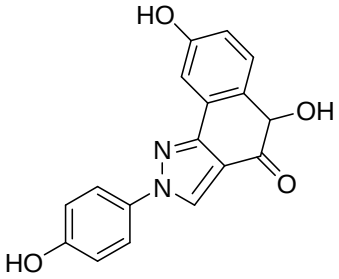
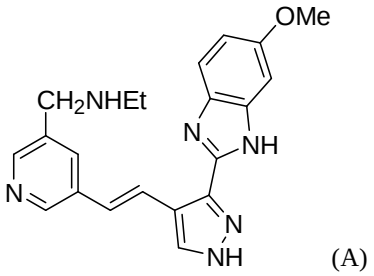
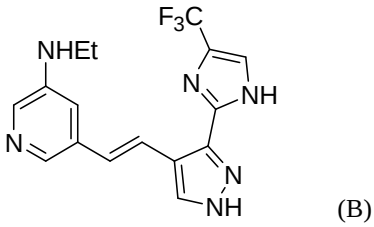
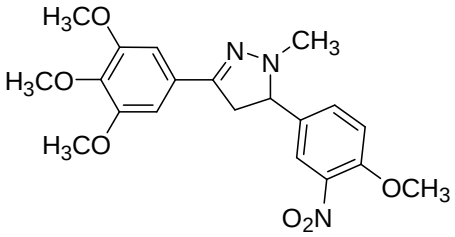
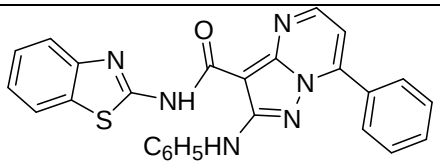
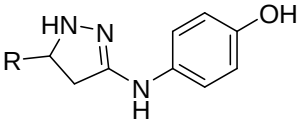
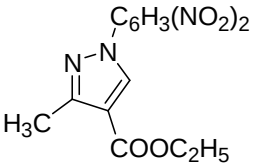
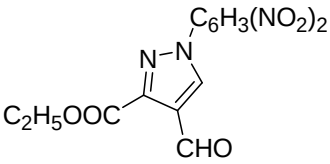
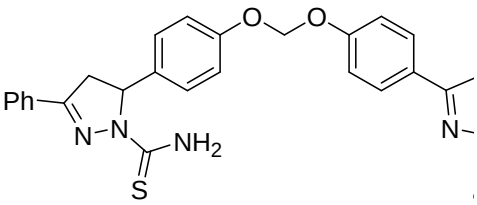
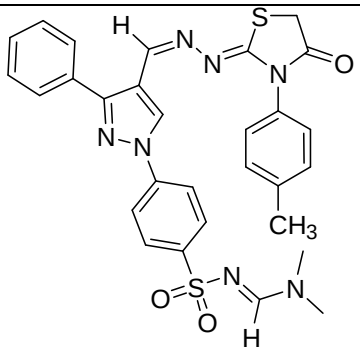
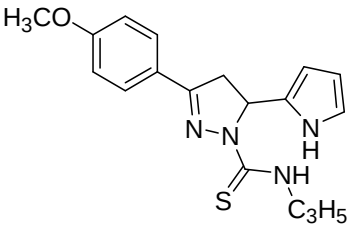
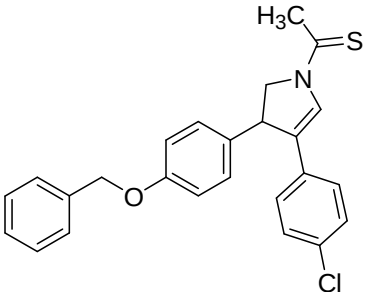
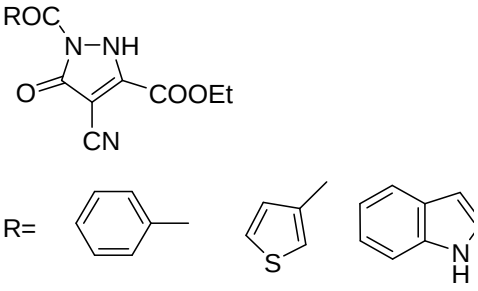
6.	Atorvastatin	(3*R*,5*R*)-7-[2-(4-Fluorophenyl)-3-phenyl-4-(phenylcarbamoyl)-5-propan-2-ylpyrrol-1-yl]-3,5-dihydroxyheptanoic acid		Pyrrole	statin
7.	Carvedilol	(±)-[3-(9*H*-carbazol-4-yloxy)-2-hydroxypropyl][2-(2-methoxyphenoxy)ethyl]amine		Carbazole	congestive heart failure
8.	Ondansetron	(*RS*)-9-methyl-3-[(2-methyl-1*H*-imidazol-1-yl)methyl]-2,3-dihydro-1*H*-carbazol-4(9*H*)-one		Imidazole	serotonin 5-HT3 receptor antagonist
9.	Cefdinir	8-[2-(2-amino-1,3-thiazol-4-yl)-1-hydroxy-2-nitroso-ethenyl]amino-4-ethenyl-7-oxo-2-thia-6-azabicyclo[4.2.0]oct-4-ene-5-carboxylic acid		Thiazole	a semi-synthetic third generation cephalosporin which is administered orally and has an extended antibacterial activity against both gram-positive and gram-negative bacteria.

Table 2: List of some new pyrazole containing compounds with their biological activity(ies).

S.No.	Reference	Compound	Biological activity
1.	Peng-cheng LV *et al.*(2010)		Antiproliferative activity against MCF-7 with IC50 0.08 µM .
2.	Michael S. Christodoulo *et al* (2010).		Anti-antiangiogenic activity. against human breast (MCF-7) and cervical (He La) carcinoma cells in vitro ($p<0.01$) by chicken chlorioallantoic membrane (CAM) assay.
3.	Ronghui Lin *et al.* (2007)	 (A)  (B)	Compound A having antiproliferative activity against HCT-116 with IC_{50} 0.19 µM; against A-375, 0.55 µM and against HeLa; 0.62 µM. Compound B having Cyclin- dependent kinase inhibitory activity with IC_{50} against cyclin-B 0.018 µM.
4.	Macro Bonesi *et al*., (2010)		Angiotensin-I-converting enzymes inhibitory activity with IC_{50} value 0.213 µM.

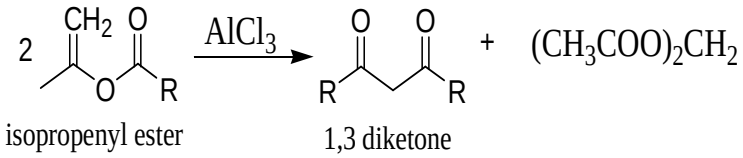
5.	Samir Bondock *et al*., (2010)		in-vitro antifungal activity with MICs (6.25 µ/ml) against *A. fumigatus* & *F. Oxysporum* comparable with Chloroamphenicol
6.	S. K. Sahu *et al*,. (2008)	 **Fig. 8** **Compounds** **R** A -4-NO_2-C_6H_4 B -2-OH-C_6H_4 C -4-Cl-C_6H_4	Antibacterial activity; against *Staphylococcus aureus, salmonella typhi & E. coli.* Antifungal activity; *against Candida albicans & Aspergillus niger* Analgesic and anti-inflammatory activity;
7.	Radhakrishnan sridhar *et al*,. (2004)	 (A)  (B)	Antibacterial activity: *Escherichia coli, Pseudomonas aeuroginosa, Enterobacter facecalis and Staphylococcus aureus* with area of zone of inhibition for compound (A) 7.8, 0.0,8.2 and 7.6 cms respectively in a conc. of 0.5mg/ml. For compound (B), the values are 8.8,2.3, 8.8 and 8.6cms respectively. Antifungal activity: against five pathogenic fungi such as, *Rhizochonia solani, Fusaricom oxysperum, Curuvularia lunata, Alernarnia alternate and Bipolaris oryzae.* The area of zone of inhibition when used in a conc. of 0.5 mg/ml are 8, 5.4, 5.3, 4.8 and 4.5 cms respectively for compound (A) and 4.2, 2.6, 3.5, 2.1 and 2.3cms. respectively for compound (B).
8.	Flora F. Barsoum *et al.*, (2009)		Anti- inflammatory activity against carrageenan-induced rat paw edema test with 79.5% inhibition of paw edema in a dose of 20 mg / kg body weight, more than that of Indomethacin (67.3%)

9.	Adnan A. bechit *et al*., (2008)		Anti-inflammatory activity by the cotton pellet granuloma method of rat paw edema bioassay; and comparable antimicrobial activity to that of ampicillin against *E.coli*.
10.	Nesrin Go¨khan-Kelekc *et al.,* (2007)		MAO-B inhibitory activity with IC_{50} value 29.13±2.56 µM and found to inhibit increased capillary permeability induced by acetic acid in mice by 38.8%.
11.	Osama I *et al*,. (2009)		Antiviral activity against a broad panel of viruses in different cell culture (HEL Cell cultures with IC_{50} value of 7 mg/ml).
12.	Mohamed Abdel Aziz *et al*., (2009)		Compounds showed anti depressant activity (using tail suspension behavioral despair test) with duration of immobility (in seconds) 183.90±9.30, 198.70±6.80, and 169.90±9.60 for compounds A, B and C respectively, comparable with Imipramine having the value 132±2.60 s.

For the synthesis of β-diketones, several synthetic routes have been developed: (1) Claisen condensation of corresponding esters with esters, or ketones with esters in the presence of sodium hydride (NaH), tetramethyl orthosilicate/ cesium fluoride, sodium ethoxide, or n-butyl lithium (Hauser CR *et al*.,1954; Boyer J *et al.*,1983; Popic VV *et al.*,1991); (2) acylations of β-alkylketones with acid chlorides in the presence of pyridine or triethylamine(Linn BO and Hauser CRJ,1956) and (3) aldol condensation of aldehydes or β-alkyl ketones to yield the 3-hydroxyl ketones, followed by an oxidation (Calter MA and Liao W, 2002). As an extension of these synthetic procedures, following paragraphs incorporate some of the published processes for the synthesis of mainly 1,3-Diketones along with the synthesis of 1, 4-diketones as well as novel β-triketones.

Starting from as early as 1969, in pursuing their studies of acylation by the agency of long chain enol ester under conditions of aluminum chloride catalyst, Rothman *et al.* (Rothman *et al.*, 1969), had discovered a simple one-step synthesis of symmetrical β-diketones. Treatment of a hexane solution of an isopropenyl ester with 0.25 to 1.0 mole of aluminum chloride formed diacylmethanes in typically 65-70% yields. The reaction mixture was a single homogenous phase mixture, and at room temperature the reaction time was 0.25 hours. Thus from the stearate, laurate, octanoate and acetate isopropenyl esters respectively were directly obtained following diacylmethans: distearoylmethane (**Ia**) R=$C_{17}H_{35}$, M.P. 77.3-77.8°; dilauroylmethane (**Ib**), R=$C_{11}H_{23}$, m.p. 53°; dioctanoylmethane (**Ic**), R=C_7H_{15}, m.p. 20-21°; and acetylacetone, (**Id**), b.p. 142° (Scheme 1).

Some Important Synthetic Processes



Scheme 1 Formation of symmetric β- diketones from corresponding isopropenyl esters.

As an exceptional behavior, enol esters, such isopropenyl stearate (II), easily form acylium ion (III) via isopropenyl stearate-aluminum chloride complex.

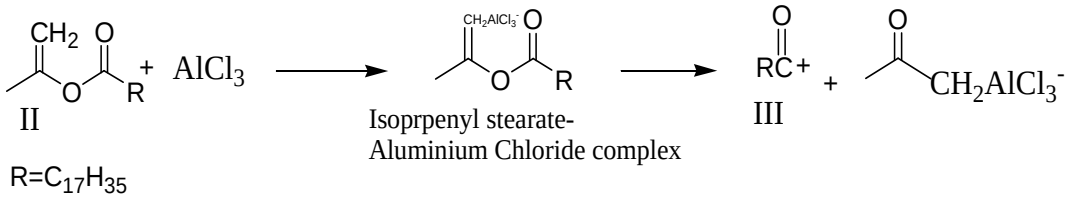


Fig 1: Acylium ion formation.

Formation of β-diketone is thus explained by combination of another molecule of isopropenyl stearate (II), with acylium ion (III) by the following mechanism:

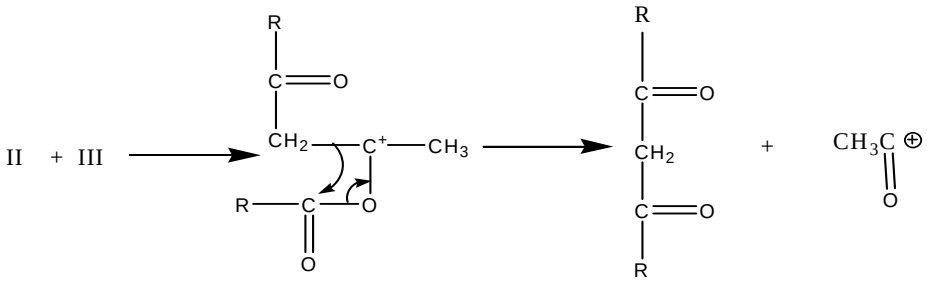
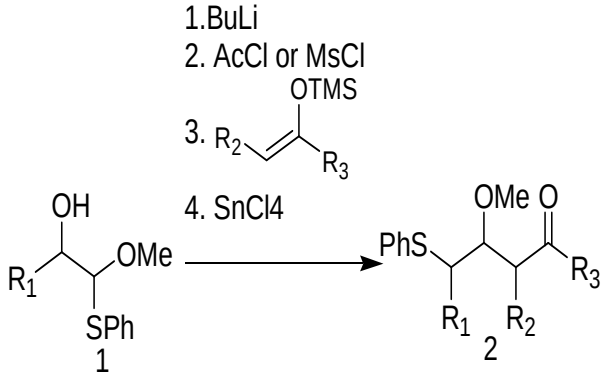


Fig 2: formation of β-diketone.

Later, Otera *et al.* (Otera *et al.*, 1989) reported a divergent synthesis of 1, 3- and 1, 4-diketones from common precursors, β-methoxy-γ-phenylthio ketones. These compounds were derived through the novel phenylthio migration reaction of the aldehyde adducts with methoxy(phenylthio)-methane upon exposure to enol silyl ethers. The compounds thus obtained were converted into 1, 3- and 1, 4-diketones.

The method had its foundation on facile one-pot synthesis of **2** through incorporation of enol silyl ethers **3** into the methoxy(phenylthio)methane-aldehyde adducts **1(**Mandai T *et al.*,1983; Rothman *et a..*, 1988; **)** induced by novel phenylthio migration (Scheme 2). Till then that was the first example of the phenylthio migration concomitant with carbon-carbon bond formation although precedent studies disclosed conversion of **1** into α-sulfenylated carbonyl compounds (Groo Ae de and Jansen BJM, 1981; Sate T *et al.*, 1988) as well as migration reaction of more simple β-hydroxy sulfides followed by dehydration giving rise to allyl sulfides (Aggarwal VK and Warren S, 1987). $SnCl_4$ proved to be more effective than other Lewis acids such as $TiC1_4$, $AlC1_3$, $TMSOT_f$, and BF_3OEt_2.



Where, R_1, R_2, and R_3 may be following groups:

R_1	R_2	R_3
Phenyl (C_6H_5)	H	H
Biphenyl	Methyl	phenyl
Isopropenyl		Methyl
		t-butyl

Scheme 2 Synthesis of β-methoxy-γ-phenylthio ketones, 2[a]

[a] Reaction conditions: 1. BuLi, CH_2Cl_2, -78-0°C, 0.5h
2. AcCl or MsCl, 0°C,1h,and
3. $SnCl_4$(1.0equiv), -78°C,

Fig.2 conceptualizes the process as a whole. The new route for 1,3- diketones stemmed from fabrication of the three components, a carbocation, a carbonyl l, l- dipole, and an enolate. Particularly worthy of note is conversion of the carbonyl function of the aldehydes into a methylene moiety. On the other hand, 1,4-diketones are assembled through the $C_1 + C_1 + C_2$ coupling mode, which has been previously prosposed (Sate T *et al.*,1988). In this instance, methoxy(phenylthio)methane works as a methylene l,l-dipole equivalent (Trost BM and Ghadiri MR, 1984) in contrast to a carbonyl l,l-dipole equivalent (Trost BM and Quayle P, 1984) in the former case. Apparently, this unique transposition of the carbonyl function results from the selective elimination of the vicinally located methoxy or phenylthio group in **1** (Otera J, 1988) coupled with the novel phenylthio migration**.**

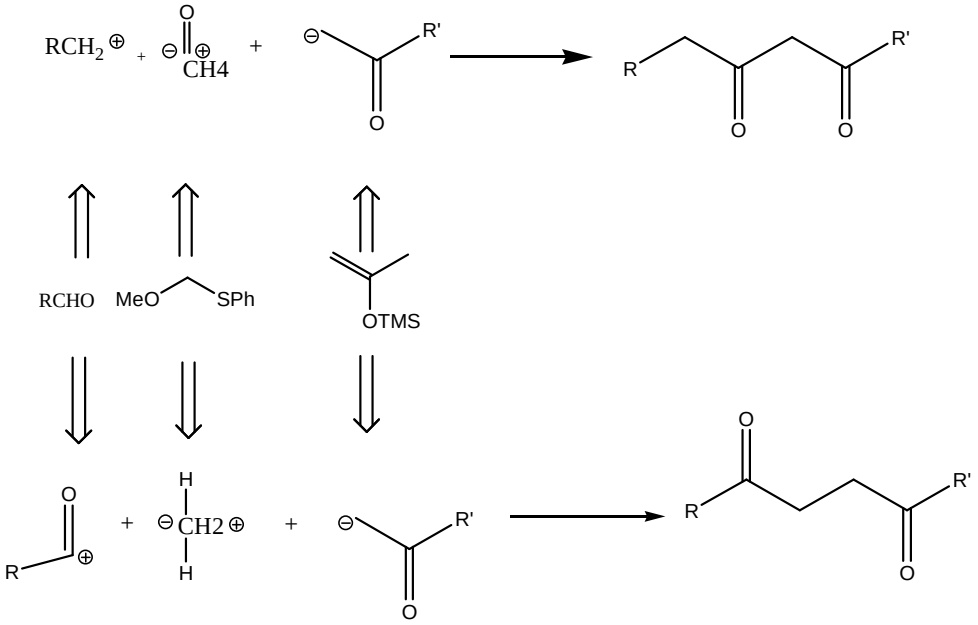
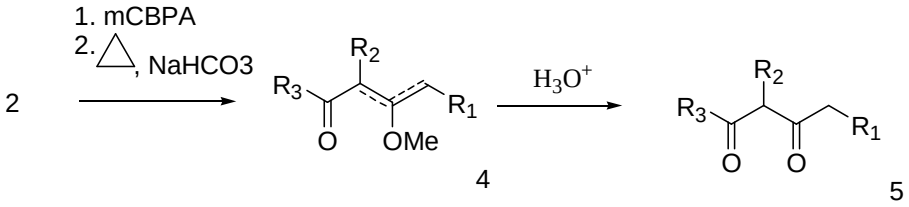


Fig.3 Mechanism of formation of 1,3- and 1,4- diketones.

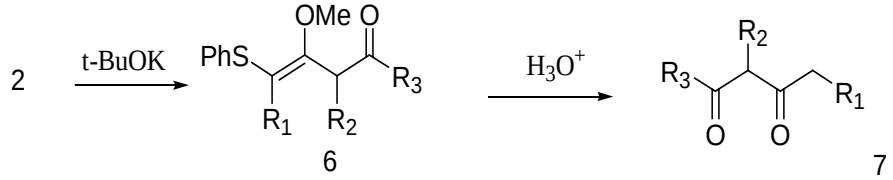
Oxidation of **2** with *m*CPBA followed by thermolysis in refluxing mesitylene and hydrolysis of the resulting enol ethers **4** provide l, 3 diketones **5** (scheme 3).



Scheme 3 Synthesis of 1,3-diketones, 5[a]

[a]Reaction conditions from **2** to **4**: mCBPA, CH_2Cl_2, -50°C, 0.5-1h,and then $NaHCO_3$,mesitylene,reflux. Reaction conditions from **4** to **5**: $ZnCl_2$,CF_3COOH-H_2O (4:1),rt.

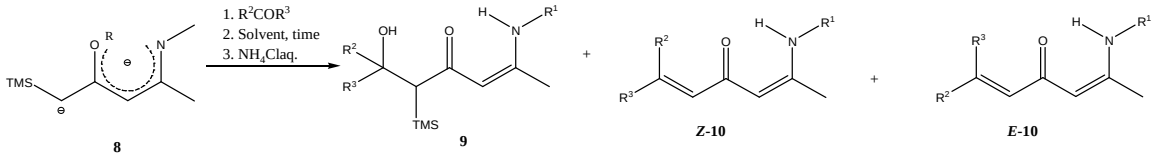
Exposure of **2** to *t*-BuOK (Takeda T, 1984) and subsequent acid-hydrolysis of the alkenyl sulfides **6**[8] led to arrive at 1,4-diketones **7** (scheme 4).



Scheme 4 Synthesis of 1,4-diketones, 7[a]

[a]Reaction conditions from **2** to **6**: *t*-BuOK, THF, -78°C, 0.5-1h. Reaction conditions from **6** to **7**:CF_3COOH-H_2O (4:1),rt.

Dalpozzo *et al.*, (Dalpozzo *et al.*, 1997) reported that dianions of α'-(trimethylsilyl)enaminones can be used as Peterson reagents in the reaction with aldehydes and ketones, to obtain α-β-unsaturated enaminones or 1,3-diketones with regio and stereocontrol of the new double bond. Authors reported the results of the addition of α'-(trimethylsilyl)enaminones N,α'-dianions to aldehydes and ketones, a new application of the classical Peterson reaction (Peterson DJ , 1968).
Hydrolysis of the obtained α'-β'-unsaturated enaminones to the corresponding diketones allows the preparation of 2,3-dihydropyranones by acidic cyclization or of β'-branched 1,3-diketones by addition of Grignard reagents (Cooke MP and Jaw JY, 1992). N,α'-Dianions **8** can be generated by reaction of α'-(trimethylsilyl)enaminones with 2.5 equivalents of LTMP in THF at 0°C for 2 h. Then the carbonyl compound is added at -78 °C, the reaction temperature allowed rising to room temperature and the mixture magnetically stirred for two hours to ensure in most cases the disappearance of the starting materials. At variance with α'-unsubstituted enaminones, a transmetalation reaction occurs with enolizable carbonyl compounds, so that either longer reaction times and excess of LTMP do not affect the amount of recovered starting materials. Product distribution depends on the reaction conditions. The presence of a lithium complexing agent such as TMEDA favours the complete elimination (Peterson DJ, 1968), while the use of THF alone could result either in a mixture of β'-hydroxysilylenaminones **9** and alkenes **10** or in the exclusive formation of product **9**.



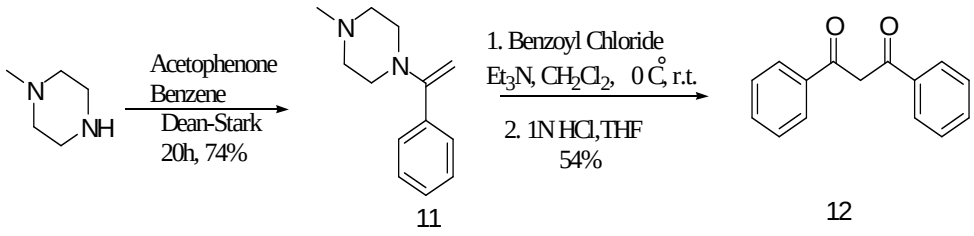
8 **9** ***Z*-10** ***E*-10**

Where, R_1, R_2, and R_3 may be following groups:

R_1	R_2	R_3
Phenyl	Phenyl	H
Isopropyl	Ethyl	Methyl

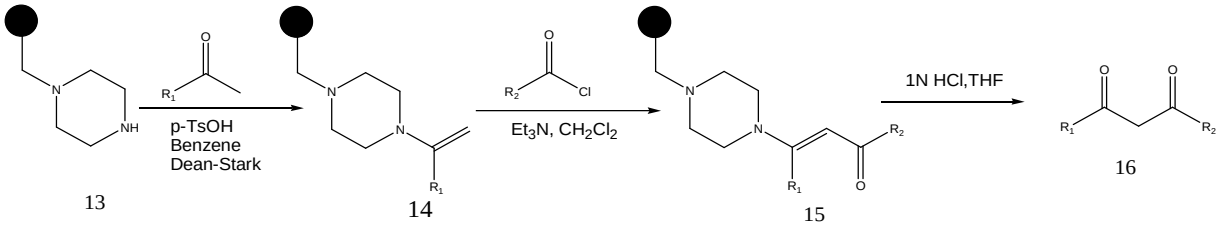
Scheme 5 Reaction of N, α'-Dianions of α'-(Trimethylsilyl)enaminones with Aldehydes and Ketones, followed by Quenching with Saturated Ammonium Chloride.

A traceless synthesis of 1, 3-diketones has been achieved by Park and Cox (Park and Cox, 2003) through enamine methodology from solid-phase organic synthesis. They used piperazine as a linker for the traceless cleavage of β-diketones from solid support. Although there are many reports of the synthesis of 1,3-diketone scaffold and its derivatives from solution phase chemistry (Hauser H *et al.*, 1954), few routes using solid phase were known, and those routes needed some improvements. For example, 1,3-diketone scaffold had been constructed in Wang or Rink amide resin through Claisen condensation, providing a starting material for pyrazole and isoxazole based heterocycle libraries (Marzinzik AL and Felder ER, 1996). However, that method, upon cleavage from solid-phase, resulted in unwanted tether such as amide (Marzinzik AL and Felder ER, 1996) or hydroxyl (Shen DM *et al.,* 2000) functional group in the product depending on the resin used. This unwanted functional group attached to the 1,3-diketones negatively influenced the formation of β-diketone-metal complexes for various materials. Furthermore, application to the synthesis of various heterocycles can result in biologically undesirable functionality in the final products. Thus, a traceless synthetic strategy for 1, 3-diketones needed to be developed to provide a large number of diverse 1, 3- diketones from solid-phase combinatorial approach. To achieve this end, enamine methodology was examined. Morpholine or pyrrolidine is widely used for the formation of ketone enamine, which, upon reaction with acyl halide, followed by hydrolysis, affords β-diketones. Since polymer supported piperazine is commercially available we chose to explore its use as a linker for enamine acylations. One example of using piperazine as a linker has been reported for the synthesis of α,β- unsaturated methyl ketones (Hird NW *et al.*, 1997). A preliminary solution phase reaction showed that β-diketone **12** was obtained from *N*-methylpiperazine through its enamine intermediate **11** (Scheme 6).



Scheme 6 Synthesis of β-diketone from *N*-methylpiperazine through its enamine intermediate.

This encouraged the researchers to further explore commercially available polymer bound piperazine **13** in this reaction. Thus, several methyl ketones were attached to piperazinomethylpolystyrene through azeotropic dehydration to afford enamine bound polymer **14**. Subsequent reaction of this polymeric enamine intermediate with substituted acyl halides provided acylated enamines **15**. After acid hydrolysis of the polymer bound acylated enamine, traceless β-diketones **16** were obtained (Scheme 7).



Where, R_1 and R_2 may be one of the following groups:

R_1	R_2
$-C_6H_5$	$-C_6H_5$
Biphenyl	$-C_6F_5$
p-CH_3-C_6H_4	*p*-Cl-C_6H_4

Scheme 7 Synthesis of traceless β-diketones from polymer bound piperazine.

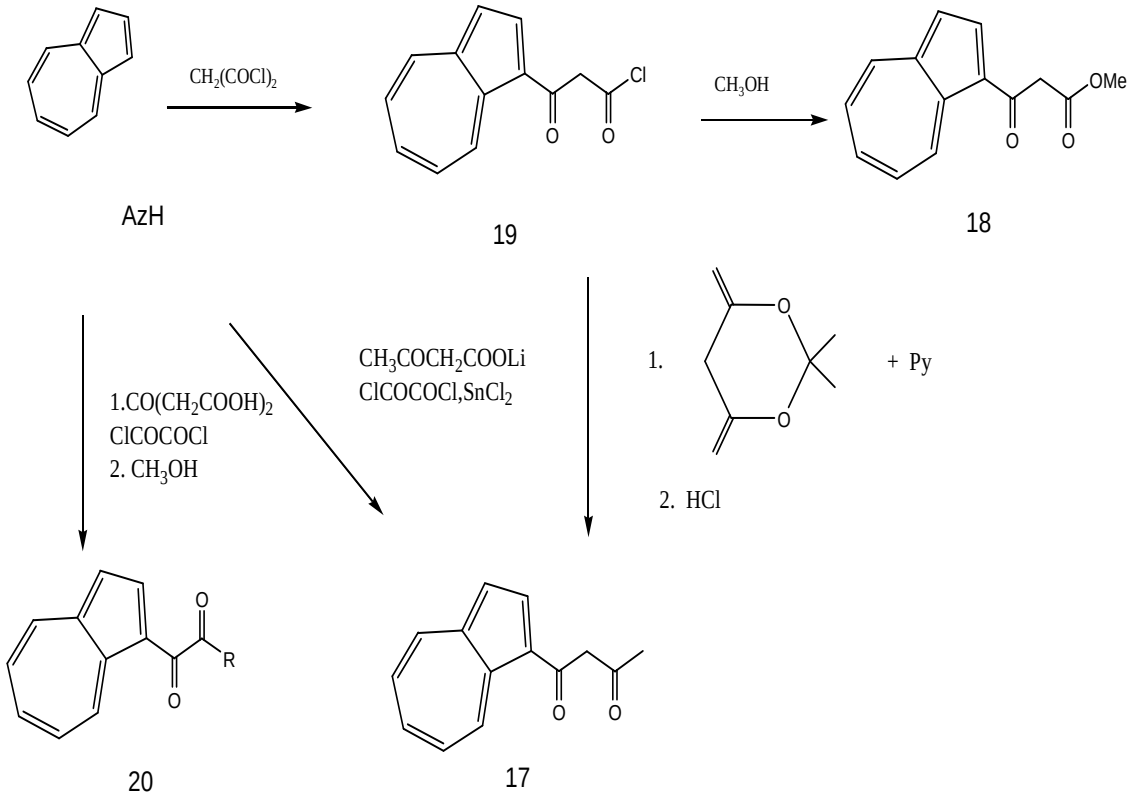
Azulenic β-diketones were synthesized by Razus *et al.* (Razus *et al.***,** 2005) in the reaction of different β-diketones with 1- azulenecarboxylic acid chloride, in the presence of MgCl2 and pyridine, as a result of condensation and subsequent acyl elimination. The obtained dicarbonyl compounds were used for the generation of azulenic pyrazoles and isoxazoles. The high polarizability of the azulene electronic system induces special features in the molecules in which it is present. As an example, the substitution of such a moiety into molecules with low electron density, or even in cations, can stabilize these compounds (Zeller KP, 1985). The inclusion of such a substituent for compounds with push-pull electronic systems is of increasing interest since many materials with valuable optical properties belong to this compound class (Asato AE *et al.*, 1996; Iftime G *et al.*, 1998; Wang P *et al.*, 1999; Lacroix PG *et al.*, 2000).The first attempt to synthesize diketone **17** is summarized in Scheme 8. For the generation of the intermediate **19** the same protocol was followed as used by Treibs for the ester **18 (**Hurd CD and Kelso CD, 1940**)**. The procedure was modified, replacing malonyl dibromide by a mixture of malonyl dichloride and gaseous HBr. The subsequent reaction of **19** with Meldrum's ester, **20 (**Obaza J and Smith FX, 1982**)**, yielded the diketone **17** in a low yield (~10 %). A low yield (also under 10%) also was obtained when the lithium salt of acetylacetic acid was reacted with azulene in the presence of oxalyl chloride (Scheme 8). The reaction of azulene with acetonedicarboxylic acid in the presence of oxalyl chloride followed by treatment with methanol afforded the methyl ester of 1- azulenoylcarboxylic acid, **5** (Scheme 8).

General procedure for preparation of dicarbonylic azulenic compounds

In a flame-heated 25 ml round-bottom flask, under an inert atmosphere, freshly calcinated $MgCl_2$ (47.5 mg, 0.5 mmol) and DCM (2 ml) were magnetically stirred. To the resulting heterogeneous mixture β-ketonic compound (0.5 mmol) was added and the flask was cooled in ice. Then pyridine (80 mg, 1.0 mmol) was added, the mixture was stirred 15 min and 1-azulenoyl chloride (obtained from 1-azulenecarboxylic acid (86 mg, 0.5 mmol) and oxalyl chloride (64 mg, 0.5 mmol) in DCM (2 ml)) was finally added. The reaction mixture was stirred 15 min at 0°C and then for several hours at room temperature. The mixture was cooled at 0°C, quenched in hydrochloric acid (3 ml, 6 M HCl) and extracted three times with diethyl ether (3 x about 2 ml). The ethereal solution was dried (Na_2SO_4), the solvent removed in vacuum and the products were separated by column chromatography on silica gel using pentane, DCM and ethyl acetate as eluents. The red or brown fractions were separated as azulencarbonyl derivatives. Azulencarboxylic acid or its magnesium salts, also colored, were eluted in several fractions. Sometimes the last fractions contained also an amount of ketone and, accordingly, they were rechromatographed.

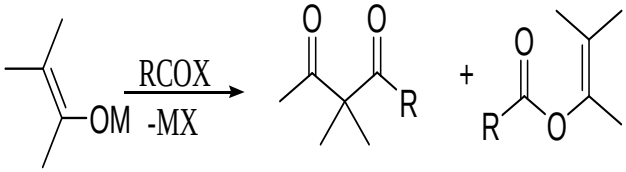
General procedure for heterocycle synthesis:

Carbonyl derivatives were dissolved in methanol at 15-20°C and then anhydrous hydrazine or an equimolar mixture of hydroxylamine and its chlorohydrate was added in a huge excess (more than 100 equivalents). The red solution was refluxed for 2 hours; however its color still remained unchanged. Then, the methanol was removed under vacuum heating for 15-30 min on a water bath to eliminate water and excess of hydrazine or hydroxylamine. As a result, the solution turned from brown-red to green or bluish-green. The obtained oil was dissolved in DCM and the products were separated by column chromatography on silica gel using as eluent a mixture of DCM and ethyl acetate (increasing the amount of ester). The different color of the reaction products allowed their easy separation.



Scheme 8: Synthesis of azulenic β-diketones

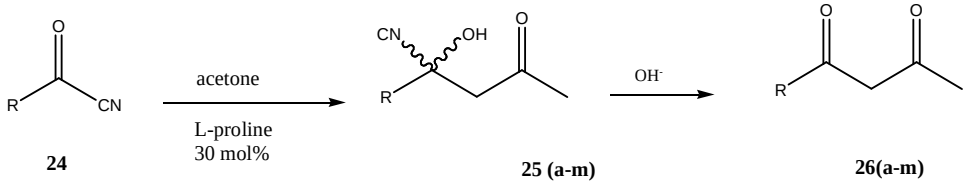
Zhang *et al*. (2005) reported the aldol-type addition of acetone towards (un)substituted benzoyl, heteroarylcarbonyl or α,β-unsaturated acyl cyanides was efficiently catalyzed by L-proline (30 mol %) to give 2-hydroxy-4-oxo-2-substituted pentanenitriles. Upon the treatment with sodium hydroxide, the adducts transformed to 1, 3-diketones in good-to-excellent yield, furnishing an efficient and convenient method for the *regioselective synthesis of 1,3-diketones*. One of the familiar syntheses of 1,3-diketones is the C-acylation of simple ketones via their metal enolates, enamines or silyl enol ethers, using acyl chlorides or cyanides as the acylating reagent, with or without catalysts. Since the ketone anions **21** are ambident, such acylating reaction often results in the formation of a mixture of C-acylated product **22** and O-acylated product **23**, which are difficult to separate (Scheme 9). Although some methods such as the reaction of ketone metal enolates with acyl chlorides or acyl cyanides (Howard AS *et al.*, 1979), the acylation of enamines (Stork G *et al.*, 1963), the direct BF_3 acylation of ketones (Mao CL *et al.*, 1969; Manyik RM *et al*., 1953), and the C-acylation of silyl enol ethers (Le Roux C *et al.*, 1996), had been reported as reactions, which preferentially lead to C-acylated ketones, the 1,3-diketones obtained are usually contaminated with variable amounts of O-acylated products.



21 22 23

Scheme 9: Formation of C-and O- acylated products

The second familiar synthesis of 1,3-diketones is the C-acylation of acetylacetone or its derivatives by acyl halides or esters followed by base-promoted cleavage of a carbonyl group. The C-acylation of acetylacetone using acyl chloride in the presence of a base, also suffered from the competition of O-acylation. For example, under phase-transfer conditions, acylation of acetylacetone and of ethyl acetoacetate with acetyl chloride and benzoyl chloride yielded O-acylated enol esters predominantly (March J, 1985; Jones RA *et al.*, 1977; Taylor EC *et al.*,1968). The chemoselectivity of such acylations depends on the nature of the solvent, electrophile, metal counterion, reaction temperature and structure of the substrate. Alan R. Katritzky reported a novel method for the preparation of 1,3-diketones from acetylacetone using the strategy of acylation–deacylation, in which, 1-acylbenzotriazoles were employed as the acylating reagents (Katritzky AR *et al.*, 2004). However, to improve the yield of this reaction is still necessary. As a versatile organocatalyst, proline has drawn much attention in recent years. Authors broaden the scope of proline-catalyzed asymmetric aldol-type addition. In the view of electron effects, the electron withdrawing cyano group in an acyl cyanide molecule would enhance the reactivity of the adjacent carbonyl carbon atom so that a proline-catalyzed aldol-type addition of acetone to acyl cyanide may occur. Indeed, benzoyl cyanide (**24**), when stirred with proline in acetone at room temperature, gave a new compound, which was identified as the expected aldol-type adduct (**25a**). After evaporation of the excess acetone, the treatment of the crude adduct **25a** with base, afforded C-acylated acetone **26a** in excellent yield, without any detectable formation of O-acylated or diacylated product. Thus proline-catalyzed aldol-type addition furnished an efficient, convenient and regio-specific method for the C-acylation of acetone, affording 1,3-diketones after a base-promoted elimination of hydrogen cyanide (Scheme 10). Encouraged by this success, a variety of acyl cyanides, including substituted benzoyl, cinnamoyl, furan-2-carbonyl cyanide were then tested.



24 **25 (a-m)** **26(a-m)**

a. R = Ph
b. R =4-CH_3-C_6H_4
c. R =2-CH_3-C_6H_4
d. R =4-CH_3O-C_6H_4
e. R =2-F-C_6H_4
f. R =4-F-C_6H_4
g. R =2-Cl-C_6H_4
h. R =4-Cl-C_6H_4
i. R =2-Br-C_6H_4
j. R =4-Br-C_6H_4
k. R =4-NO_2-C_6H_4
l. R = Ph-CH=CH
m. R =furan-2-yl

Scheme 10: L-Proline catalyzed acylation of acetone with acyl cyanides as the acylating agents.

A variety of proline derivatives were also tested as catalysts for this reaction under standard conditions which may be obtained from the references cited. A mechanism, for the aldol addition of acetone to aldehyde, was proposed, as shown in Fig. 3. We supposed that acetone was activated by formation of an enamine with proline. An acyl cyanide molecule was pulled close to the enamine by the proline hydroxyl group through hydrogen- bonding interaction. The enamine attacked the carbonyl group of the acyl cyanide acceptor, forming the key intermediate, which then eliminated HCN on treating with sodium hydroxide to afford the 1,3-diketone (Zhang Y *et al*., 2005).

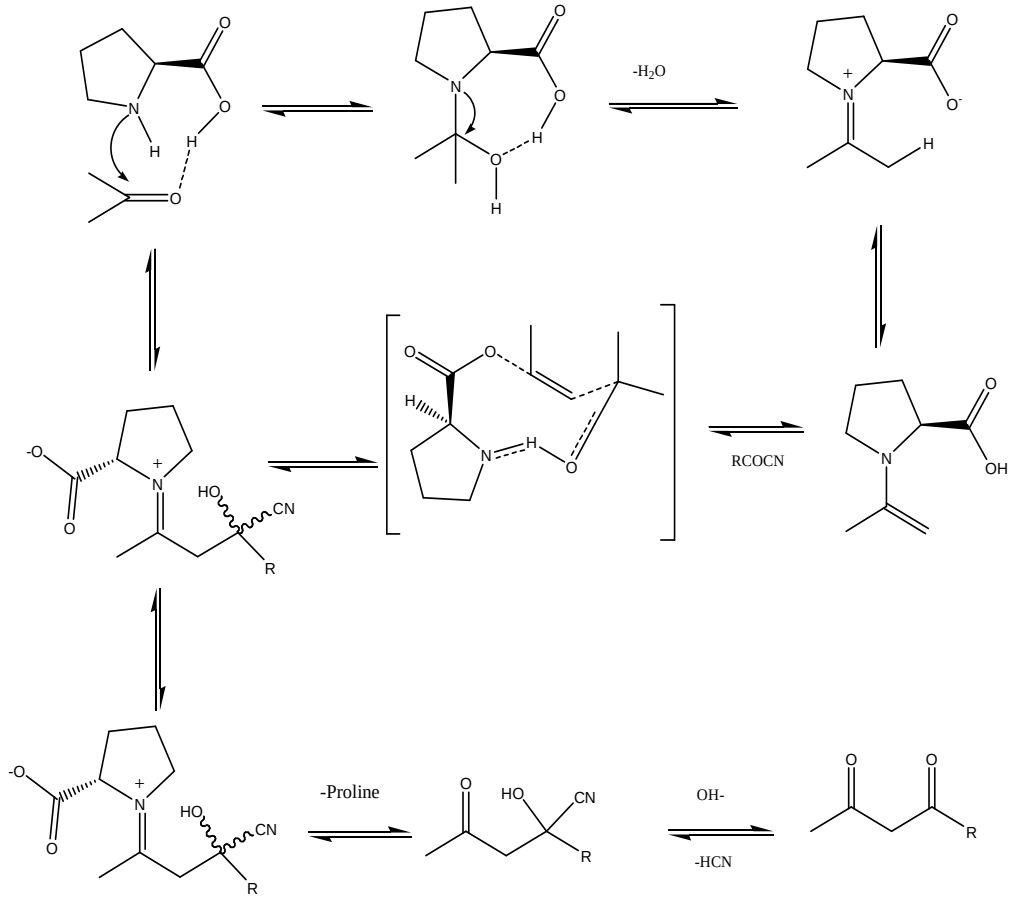
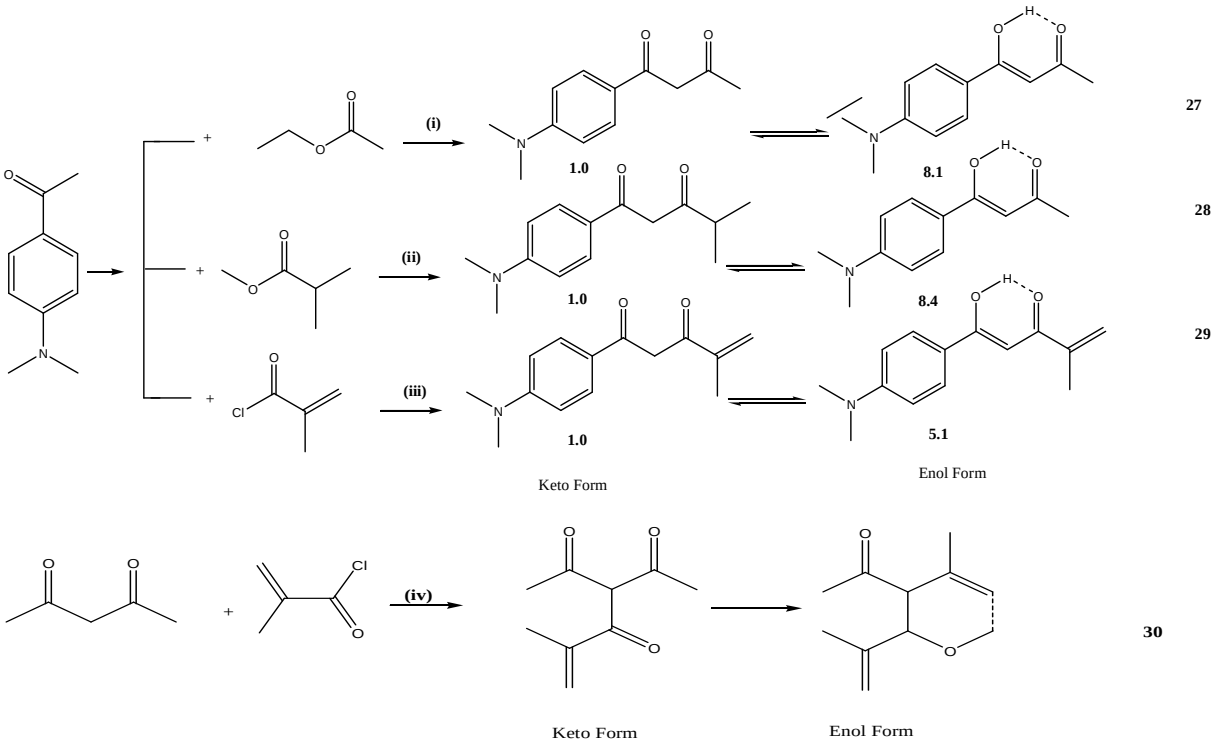


Fig 4: Proposed mechanism of L-Proline-catalyzed formation of diketones

Saturated and unsaturated β-diketones bearing 4-N, N-dimethylaminophenyl substituent and a novel β-triketone were synthesized by Zhang *et al*. (2006). These β-diketones exists in both cis-enol and keto forms in solution, and their relative contents were determined by ^{1}H NMR measurements. In contrast, for the β-triketone, only enol form was observed in a solution. β-Diketones **27** and **28** were synthesized by Claisen condensation of 1-(4-(dimethylamino) phenyl) ethanone with ethyl acetate and methyl pivalate, respectively, using dibenzo-18-crown-6 and ethyl ether/diethylene glycol dimethyl ether (5/1, v/v) as solvents in the presence of sodium hydride (NaH) as shown in Scheme 11. The synthesis of β-diketones **29** and **30** is based on an improved acylation employing diethyl ether/diethylene glycol dimethyl ether (4/1, v/v) as solvent under strong basic conditions, that is sodium amide (NaNH2) for **29** and magnesium ethanolate ($Mg(OC_2H_5)_2$) for **30.** There are few reports on the acylation reaction under such strong basic conditions.



Scheme 11 Synthetic routes to the saturated β- Diketones 27 and 28 , the unsaturated β- Diketone 29, and Triketone,30.

Reagents and conditions: (i) NaH, dibenzo-18-crown-6, rt; (ii) NaH,Et_2O/diglyme(5/1,v/v), rt; (iii) $NaNH_2$, Et_2O/diglyme(4/1,v/v), ; (iv) $Mg(OC_2H_5)_2$, Et_2O/EtOH(4/1,v/v), 0-5°C.

Conclusion

1,3-diketones, 1,4-diketones as well as β-triketones are useful synthon for preparation of a variety of heterocycles which in turn are important intermediates for drug synthesis. While 1,3-diketones are versatile precursors to heterocycles such as pyrazoles, isoxazoles etc., the 1,4-Diketones are useful precursors to heterocycles via the Paal-Knorr Synthesis, which gives furans, pyrroles, and thiophenes. The condensation of 1,4-diketones (and related substrates) with hydrazines afford dihydropyridazines, which can be converted to pyridazines and β- triketones are important for the preparation of tricyclic heterocycles like indenopyrazoles, indenodiazepines,indenopyrimidines etc. Various synthetic procedures presented in this review are of importance for a medicinal chemist, according to the need e. g., while one step short and simple method for preparation of β-diketones is form isopropenyl esters, β-methoxy-γ-phenylthio

ketones may serve as common precursor for the synthesis of both of the 1, 3- and 1, 4-diketones. Regioselective synthesis of α-β-unsaturated enaminones or 1,3-diketones can be achieved through dianions of α'-(trimethylsilyl)enaminones, a traceless synthesis of 1, 3-diketones has been achieved using piperazine as a linker through enamine methodology. Azulenic β-diketones synthesized by the reaction of different β-diketones with 1- azulenecarboxylic acid chloride are important for heterocyclic chemistry, and a versatile organocatalyst, proline, has shown to catalyze the aldol-type addition of acetone towards (un)substituted benzoyl, heteroarylcarbonyl or α,β-unsaturated acyl cyanides to form regioselective 1,3-diketones. Synthetic routes to the saturated β-Diketones , the unsaturated β- Diketone , and Triketone, from a common precursor has also been included in this review. The preparation of such synthetically important diverse compounds may help a research scientist in the area of heterocyclic as well as medicinal chemistry.

"Cite this Article"

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