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An Efficient Synthesis of Biopertinent Dihydropyrimidine (thi) one Derivatives *via* Three-component One-pot Synthesis Catalyzed by Tetrachlorosilane

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SERIES of dihydropyrimidine(thi)one derivatives were prepared, in good yields at room temperature by using a modified Biginelli reaction. The products were obtained through a one-pot three-component coupling of β-diketones, aldehydes and urea (or thiourea) in the presence of a catalytic amount of tetrachlorosilane (TCS). The effect of catalyst type, molar ratios of reactants and solvent type were also investigated; best results were obtained when TCS was employed as a catalyst and CH_2Cl_2 as a solvent at room temperature.

Keywords: Three-component, Dihydropyrimidinones, Biginelli reaction and Tetrachlorosilane.

The Biginelli reaction has been reviewed[1]. Several improved protocols for the preparation of dihydropyrimidines (DHPMs) have been reported, either by modification of the classical one-pot condensation approach itself [2-6], or by the development of novel approach but more complex, multi-step strategies[7]. However, some of the reported methods suffer from drawbacks such as unsatisfactory yields, cumbersome product isolation procedures and environmental pollution[6,8–13]. Moreover, some of the methods are only practical for aromatic aldehydes[6,14]. Furthermore, in order to improve the efficiency of Biginelli reaction, a variety of catalysts have been reported of which $H_4PMo11VO40$[15], Dowex-50W[16], $H_3PW_{12}O_{40}/SiO_2$[17], $MgBr_2$[18], polymer supported 4-aminoformoyldiphenylammonium triflate[19], $NaHSO_4/SiO_2$[20], $FeCl_3$[21], $ZrCl_4$[22], $Cu(OTf)_2$[23], $Bi(OTf)_3$[24], yutterbium triflate [25], NH_2SO_3H[26], 12-Molybdopho sphoric acid[27], natural HEU type zeolite[28], $Sr(OTf)_2$[29], covalently anchored sulfonic acid onto silica[30], $ZrOCl_2.8H_2O$[31], silica triflate[32], $Fe(HSO_4)_3$[33],TCICA[34], PPh_3[35], CaF_2[36], [bmim]BF_4-immobilized Cu(II) acetylacetonate[37], [bmim][$FeCl_4$][38], ionic liquids under ultrasound irradiation[39], melamine trisulfonic acid[40], silica sulfuric acid [41] are examples.

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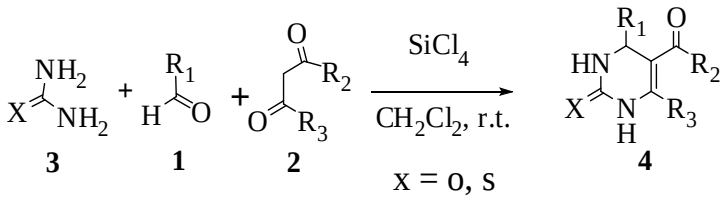
Dihydropyrimidinones are significant class of organic compounds, with prominent biological activities. Several functionalized dihydropyrimidines have been found to exhibit a wide spectrum of biological effects including antiviral, antitumor, antibacterial and anti-inflammatory activities[42]. In addition, 4-aryldihydropyrimidines have emerged[43] as potent calcium channel blockers, antihypertensive, α_{1a}-adrenergic antagonists and neuropeptide antagonists. Furthermore, dihydropyrimidinone-5-carboxylate core unit is found in many marine natural products[44] including Batzelladine alkaloids, which are potent-HIV gp-120-CD_4 inhibitors. A number of novel 5-(CF_3CO)dihydropyrimidine(thi)ones have been synthesized using Trifluoromethyl-1,3-diones as reactants in the Biginelli reaction promoted by Me_3SiCl. Thus, a set of new CF_3-containing dihydropyrimidine(thi)one derivatives was obtained[45-47].

Thiourea was also used as one of the ingredients with similar success to provide the corresponding dihydropyrimidin-2(1*H*)-thiones, which are also of interest for their biological activities. A novel and efficient task-specific ionic liquid synthesis of Biginelli compounds has been developed. Ionic liquid-phase bound acetoacetate reacted with (thio)ureas and various aldehydes with ionic liquid-phases supported 3,4-dihydropyrimidine-2-(thi)ones. The desired 3,4-dihydropyrimidine-2-(thi)ones were easily separated from the ionic liquid-phase by trans-esterification under mild conditions in good yields and high purity[48]. An effective procedure for Biginelli's three component condensation producing 3,4-dihydropyrimidin-2(1*H*)-thiones by employing calcium fluoride has been carried out. In order to extend our knowledge in structure-activity relationship, all newly synthesized compounds are tested for their *in vitro* antibacterial and antifungal activities and the influence of some structural variations was evaluated by varying the substituent at the phenyl group in the synthesized compounds[49-53]. Therefore, a need still exists for versatile, simple and environment friendly processes whereby DHPMs may be formed under milder and practical conditions, versatile catalytic systems and thus, there is a room for further improvement toward milder reaction conditions, variations of substituents in all three components and better yields.

As a part of ongoing research program directed towards the development of new and rapid synthetic methods using silicon reagents for the construction of biologically active structural motifs[54], it was intended, in the present work, to develop rapid, efficient and inexpensive protocol for a one-pot synthesis of dihydropyrimidine(thi)one derivatives based on the Biginelli reaction using tetrachlorosilane as heterogeneous catalyst. As compared to expensive Lewis acid catalysts, such as lanthanide chlorides and lanthanide triflates, tetrachlorosilane (TCS) is inexpensive and can be prepared very easily. The most important and salient feature of the present reaction is using very small amount of a cheap and simple chlorinated solvent. Moreover, no side products were observed in these reactions. Furthermore, the reaction can be scaled up to a multigram scale. This method allowed obtaining excellent yields of the required product in shorter reaction times as compared to those of classical methods.

Results and Discussion

1,4-Dihydropyrimidinones (DHPMs) comprise of a pyrimidine scaffold having resemblance with structures of the nucleic acid bases found in DNA and RNA. Their involvement as bases in nucleic acids has a great significance in drug design. Biginelli dihydropyrimidinone derivatives are considered as structural analogs of Monastrol, a known human kinesin Eg5 inhibitor. Racemic dihydropyrimidinone is considered to be an allosteric inhibitor of the antibody # 7625 Eg5 and unlike taxanes, it is nontoxic to neuron cells. Monastrol is the only cell-permeable molecule currently known to specifically inhibit mitotic kinesin Eg5 and can therefore be considered as a leader for the development of new anticancer drugs[55a]. Several marine natural products with interesting biological activities containing the dihydropyrimidine-5-carboxylate core have been isolated. Most notably among these are the Batzelladine alkaloids A and B which inhibit the binding of HIV envelope protein gp-120 to human CD4 cells and, therefore, are potential new leads for AIDS therapy[55b]. Silica chloride is one of the most versatile and utilized catalyst for the selective construction of heterocyclic ring systems, in particular for the synthesis of 3,4-dihydropyrimidinones[56]. To the best of our knowledge, Biginelli-type reactions catalyzed by silicon reagents have been rarely reported[57]. In the present work, dihydropyrimidin-2(1*H*)- (thi)ones, (4) were synthesized in good yield *via* a three-component, one-pot reaction of aromatic aldehyde (1), 1,3-diketone (2) and urea (or thiourea) (3) in methylene dichloride as a solvent in the presence of catalytic amounts of tetrachlorosilane (TCS) (Scheme 1).



Scheme 1. Synthesis of dihydropyrimidin ones.

As a part of ongoing study to investigate the optimum conditions for the three-component Biginelli condensation catalyzed by TCS, $FeCl_3$, $ZnCl_2$ and $SnCl_2$ in the present work was endeavored by examining the conditions required for the reaction involving thiophen-2-carbaldehyde, thiourea and ethyl acetoacetate to afford the 5-ethoxycarbonyl-6- methyl-4- (2-thienyl)-3,4- dihydropyrimidin-2(1H)-thione (4aa) in some selected solvents. A summary of the results obtained is provided in Table 1.

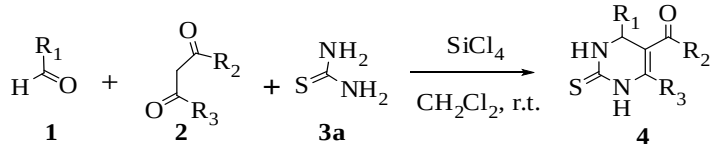
TABLE 1. Effect of catalysts and solvents on the yield and reaction time of the one-pot synthesis of 5-ethoxycarbonyl-6- methyl-4- (2-thienyl)-3,4-dihydropyrimidin-2 (1H)-thione(4aa).

Entry	Catalyst	Solvent	Time (h)	Yield (%)
1	TCS	DMF	10	15
2	TCS	THF	10	Nil
3	TCS	$CHCl_3$	5	82
4	TCS	CH_2Cl_2	3	89
5	$FeCl_3$	CH_2Cl_2	10, Δ	24
6	$ZnCl_2$	CH_2Cl_2	10, Δ	52
7	$SnCl_2$	CH_2Cl_2	10, Δ	58

Δ heat (60 -70 ºC).

Data in Table 1 revealed that, the reaction of ethylacetoacetate, thiophen-2-carbaldehyde and thiourea as a model example (1 equiv-each), proceeds in the presence of tetrachlorosilane ($SiCl_4$) at room temperature in various solvents. Chlorinated solvents such as CH_2Cl_2 or $CHCl_3$ were found to be effective solvents. The reaction was not compatible with solvents such as DMF (15% yield) or THF (which completely inhibited the reaction). Thus, the best results obtained were when TCS was employed as a catalyst and CH_2Cl_2 as solvent (entry 4, afforded the desired product in high yield (89%). Thus, it was prompted to explore the potential of using this protocol for the synthesis of various dihydropyrimidinones and dihydropyrimidinthiones (56-92% yields). The reactions proceeded smoothly by stirring in chloronated solvent at room temperature and were completed within the required time. Tables 2 and 3 show the generality of the present protocol, which is equally effective for urea or thiourea and also the selected aldehyde. Under these conditions, the yields were significantly better in comparison with the classical Biginelli procedure. In all cases, the desired dihydropyrimidine-2-(thi)one were the sole products and no by-products were observed. The experimental procedure is very simple and convenient.

The results clearly indicated the generality and scope of the reaction with respect to various aromatic and hetero-aromatic aldehydes. Noteworthy to report is that data depicted in Table 2 showed that bulky aldehydes gave lower dihydropyrimidinoes yield due to their steric hindrance compared to homocyclic and hetero-aromatic aldehydes.



1 **2** **3a** **4**

1a, R_1 =2-thienyl **2a**, R_2 = -OEt, R_3 = -CH_3
1b, R_1 =1-naphthyl **2b**, R_2 = -CH_3, R_3 = -CH_3
1c, R_1 = 2-naphthyl **2c**, R_2 = -C_6H_5, R_3 = -CH_3

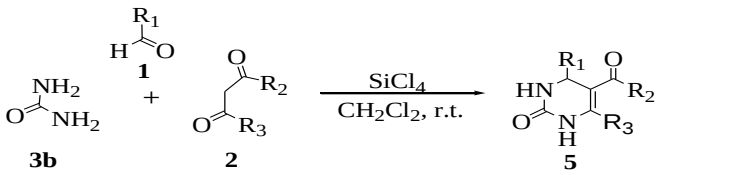
4aa, 4ab, 4ac, 4ba, 4bc, 4ca, 4cb

Scheme 2.

TABLE 2. Reaction of thiourea (3a) with various aldehydes and 1,3-diketones.

Entry	R_1	R_2	R_3	Product	Time (h)	Yield[b] (%)	Mp[c] (°C)	
							found	reported
1	2-thienyl	-OEt	$-CH_3$	4aa	3	89	213-215	215-216[58]
2	2-thienyl	$-CH_3$	$-CH_3$	4ab	4	86	222-224	--
3	2-thienyl	C_6H_5-	$-CH_3$	4ac	5	81	235-235	--
4	1-naphthyl	-OEt	$-CH_3$	4ba	6	79	218-220	--
5	1-naphthyl	C_6H_5-	$-CH_3$	4bc	8	75	295(dec.)	--
6	2-naphthyl	-OEt	$-CH_3$	4ca	5	81	185-186	188[59]
7	2-naphthyl	$-CH_3$	$-CH_3$	4cb	6	76	236	238-240[59]

[c] Melting points are uncorrected
[b] Isolated yield



1d, R_1 = furyl
1e, R_1 = 9-anthryl
1f, R_1 = phenyl
1g, R_1= 4-Cl-C_6H_4
1h, R_1= 4-Br-C_6H_4

2d, 1,3-indandione
2e, dimedone

5aa, 5ab, 5da, 5ba, 5bd, 5ea, 5ge, 5he

Scheme 3

TABLE 3. Reaction of thiourea (3a) with various aldehydes and 1,3-diketones.

Entry	R_1	R_2	R_3	Product	Time (h)	Yield[b] (%)	Mp[c] (°C)	
							found	reported
1	2-thienyl	-OEt	$-CH_3$	5aa	3	92	212-213	215-217[58]
2	2-thienyl	$-CH_3$	$-CH_3$	5ab	4	88	220-221	--
3	2-furyl	-OEt	$-CH_3$	5da	5	58	205-206	206-208[59]
4	1-naphthyl	-OEt	$-CH_3$	5ba	6	83	242-244	247-248[60]
5	1-naphthyl	1,3-indandione		5bd	9	56	236-238	--
6	9-anthryl	-OEt	$-CH_3$	5ea	7	74	248-249	251[60]
7	4-Cl-C_6H_4-	demidone		5ge	4	81	195	196-198[61]
8	4-Br-C_6H_4-	demidone		5he	5	80	>300	>300[62]

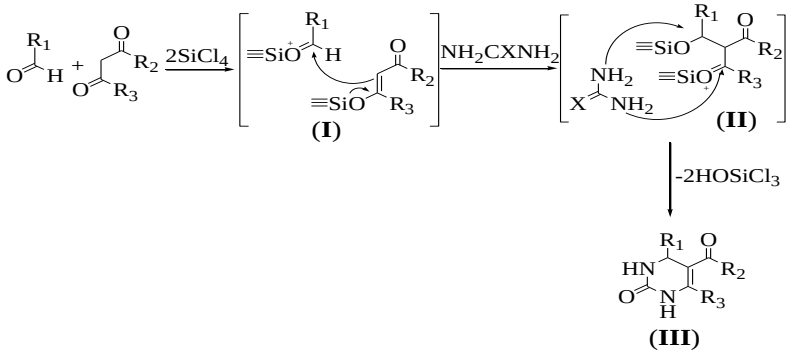
[c] Melting points are uncorrected
[b] Isolated yield

Recently, it has been reported that using thiourea and ethylacetoacetate increased reaction time for affording some dihydropyrimidinethiones, reduced the efficiency of Biginelli reaction. This is related to the low nucleophilic

property of thiourea compared to urea at intermediate state[62]. However, it was found in the present work the desired dihydropyrimidinethiones (4) were obtained in 3-8h and 75-89% yield as shown in Table 2. In comparison the dihydropyrimidinones (5) were formed in 3-9 h with 56-92% yield as given in Table 3.

The structures of the obtained dihydropyrimidinones and dihydropyrimidinthiones were confirmed by spectroscopic methods and elemental analysis Thus, the structure of 5-acetyl -6-methyl-4-(2-thienyl)-3,4-dihydropyrimidin-2(1H)-thione (4ab) was elucidated by its IR spectrum which showed peaks at ν = 3274, 3167 and 1662 cm^{-1} corresponding to (2NH) and α,β-unsaturated carbonyl groups, respectively; ^{1}H NMR spectrum revealed clearly two signals for exchangeable protons of (2NH) at δ_H = 9.85-10.41, multiplet for three aromatic protons at δ_H = 6.94-7.41, singlet signals for the protons CHNH at δ_H = 5.30, two singlet signals for $2CH_3$ at δ_H = 2.31, 2.21ppm; ^{13}C NMR spectrum for (4ab) showed two characteristic signals at δ = 196.30, 184.20, for C=O and C=S, at 150.20, 113.52 for C=C in pyrimidine ring, at 139.3, 126.5, 125, 123.4 for thiophene ring carbons, at 53.60 charcteristic signal for saturated carbon in pyrimidine ring, at 22.70, 18.22 for two carbons in $2CH_3$.

A plausible mechanism for this reaction involves the formation of the enolizable 1,3-diketone and polarized aldehyde by joining with two molecules of $SiCl_4$; these two active intermediates (I) interact with each other to form intermediate (II) which easily condenses with urea (thiourea) to form pyrimidine ring (III) as follows:



Scheme 4. Suggested mechanism.

Conclusion

In conclusion, the present protocol provides an efficient and improved modification of the Biginelli reaction. Mild reaction conditions, ease of workup, high-satisfactory yields, and stability and recyclability of tetrachlorosilane reagent are features of this protocol. Moreover, this method has the ability to tolerate a wide variety of substituents in all three components. The results are reproducible and the reactions can be carried out on a gram scale.

Experimental

Microanalyses were carried out by the Micro Analytical laboratory, National Research Centre, Cairo, Egypt. Infrared spectra (KBr-disc) were recorded using a Jasco FT/IR-300E spectrometer. ^{1}H NMR and ^{13}C NMR spectra were measured in $CDCl_3$ using Varian Mercury 300 MHz and Varian Gemini 200 MHz with chemical shifts using TMS as standard solvent. Mass spectra were recorded on a GC/MS Finnigan SSQ 7000 spectrometer. All reactions were carried out under atmospheric conditions at room temperature. Tetrachlorosilane (TCS) was obtained from commercial sources. Anhydrous zinc chloride was used as obtained from Aldrich. The solvents were distilled and dried before use. Reactions were monitored by TLC on 0.25 mm Merck Silica gel sheets (60 GF 354) (4 × 2 cm) and the spots were detected with UV light.

General procedure

In a dry two-necked round bottomed flask equipped with a rubber septum, a magnetic stirring bar and a dry condenser, a mixture of diketone (10 mmol), aldehyde (10 mmol), urea (thiourea) (10 mmol), in CH_2Cl_2 (20 ml) was allowed to stir with exclusion of moisture at room temperature for 5 min. Tetrachlorosilane (5 mmol) was then added and the mixture was stirred for the specified time as shown in Tables 2 and 3. At the end of the reaction, the mixture was poured onto ice–cold water (~100 ml), neutralized with aq. Na_2CO_3, extracted with $CHCl_3$ (3 x 30 ml) and the extract dried over anhydrous Na_2SO_4. The pure solid was filtered, washed with methanol (3X10 ml) and dried under vacuum. This procedure was followed for the preparation of compounds (4) and (5) listed in Tables 2 and 3, respectively. Spectral and analytical data for examples of these products are given below:

5-Ethoxycarbonyl-6- methyl-4- (2-thienyl)-3,4- dihydropyrimidin-2(1H) - thione (4aa)

IR (KBr) ν (cm^{-1}): 3304, 3180, 1680, 1656, 1568. ^{1}H NMR δ_H (300MHz, DMSO-d_6): δ 1.21 (t, 3H, J = 7.0 Hz, CH_3), 2.32 (s, 3H, CH_3), 4.12 (q, 2H, J = 7.0 Hz, OCH_2CH$_3$), 5.49 (d, 1H, J = 10.5 Hz, CH), 6.96-7.44 (m, 3H, ArH) 9.82 (s, 1H, NH), 10.52 (s, 1H, NH). MS (EI 70 ev) m/z: 282 (M^+). Anal. (%): Calcd for $C_{12}H_{14}N_2O_2S_2$ (282.05): C, 51.04; H, 5.00; N, 9.92; S, 22.71 Found: C, 51.00; H, 4.94; N, 9.80; S, 22.00.

5-Acetyl-6-methyl-4-(2-thienyl)-3,4-dihydropyrimidin-2(1H)-thione (4ab)

IR (KBr) ν (cm^{-1}): 3274, 3167, 1662, 1610, 1570. ^{1}H NMR δ_H (300MHz, DMSO-d_6): δ 2.21 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 5.30 (d, 1H, J = 10.4 Hz, CH), 6.94-7.41 (m, 3H, ArH) 9.85 (s, 1H, NH), 10.41 (s, 1H, NH). ^{13}C NMR (300 MHz, DMSO-*d6*): δ 196.30, 184.20, 150.20, 139.3, 126.5, 125, 123.4, 113.52, 53.60, 22.70, 18.22. MS (EI 70 ev) m/z: 252 (M^+). Anal. (%): Calcd for $C_{11}H_{12}N_2OS_2$ (252.04): C, 52.35; H, 4.79; N, 11.10; S, 25.41 Found: C, 52.22; H, 4.74; N, 10.80; S, 25.20.

5-Benzoyl-6-methyl-4-(2-thienyl)-3,4-dihydropyrimidin-2(1H)-thione (4ac)

IR (KBr) ν (cm^{-1}): 3259, 3159, 1655, 1574. ^{1}H NMR δ_H (300MHz, DMSO-d_6): δ 2.25 (s, 3H, CH_3), 5.52 (d, 1H, J = 10.4 Hz, CH), 6.95-7.97 (m, 8H, ArH), 9.81 (s, 1H, NH), 10.50 (s, 1H, NH). MS (EI 70 ev) m/z: 314 (M^+). Anal. (%): Calcd for $C_{16}H_{14}N_2OS_2$ (314.05): C, 61.12; H, 4.49; N, 8.91; S, 20.40 Found: C, 61.7; H, 4.41; N, 8.85; S, 20.34.

5-Ethoxycarbonyl-6-methyl-4-(1-naphthyl)-3,4-dihydropyrimidin-2(1H)-thione (4ba)

IR (KBr) ν (cm^{-1}): 3300, 3178, 1685, 1648, 1580. ^{1}H NMR δ_H (300MHz, DMSO-d_6): δ 0.90 (t, 3H, J = 7.0 Hz, CH_3), 2.33 (s, 3H, CH_3), 3.85 (q, 2H, J = 6.9 Hz, O$CH_2$$CH_3$), 6.04 (s, 1H, CH), 7.35-8.30 (m, 7H, ArH) 9.24 (s, 1H, NH), 10.21 (s, 1H, NH). MS (EI 70 ev) m/z: 326 (M^+). Anal. (%): Calcd for $C_{18}H_{18}N_2O_2S$ (326.11): C, 66.23; H, 5.56; N, 8.58; S, 9.82. Found: C, 66.15; H, 5.50; N, 8.53; S, 9.73.

5-Benzoyl-6-methyl-4-(1-naphthyl)-3,4-dihydropyrimidin-2(1H)-thione (4bc)

IR (KBr) ν (cm^{-1}): 3270, 3175, 1648, 1555. ^{1}H NMR δ_H (300MHz, DMSO-d_6): δ 2.55 (s, 3H, CH_3), 5.50 (s, 1H, CH), 7.08-8.66 (m, 12H, ArH), 9.34 (s, 1H, NH), 10.05 (s, 1H, NH). MS (EI 70 ev) m/z: 357 (M^+). Anal. (%): Calcd for $C_{22}H_{18}N_2O_2$ (358.11): C, 73.71; H, 5.06; N, 7.82; S, 8.95. Found: C, 73.66; H, 5.01; N, 7.75; S, 8.87.

5-Acetyl-6-methyl-4-(2-thienyl)-3,4-dihydro-1H-pyrimidin-2-one (5ab)

IR (KBr) ν (cm^{-1}): 3278, 3169, 1666, 1610, 1575. ^{1}H NMR δ_H (300MHz, DMSO-d_6): δ 2.22 (s, 3H, CH_3), 2.33 (s, 3H, CH_3), 5.30 (d, 1H, J = 10.2 Hz, CH), 6.92-7.50 (m, 3H, ArH) 9.88 (s, 1H, NH), 10.56 (s, 1H, NH). MS (EI 70 ev) m/z: 236 (M^+). Anal. (%): Calcd for $C_{11}H_{12}N_2OS_2$ (236.29): C, 55.91; H, 5.12; N, 11.86; S, 13.57 Found: C, 55.86; H, 5.08; N, 11.82; S, 13.52.

4(1-Naphthyl)- 3,4-hydro-1H-indeno[1,2-d]pyrimidin-2,5-dione (5bd)

IR (KBr) ν (cm^{-1}): 3392, 3207, 1671, 1613. ^{1}H NMR δ_H (300MHz, DMSO-d_6): δ 5.79 (s, 1H, CH), 7.14-8.32 (m, 11H, ArH), 9.57 (s, 1H, NH), 10.07 (s, 1H, NH). MS (EI 70 ev) m/z: 326 (M^+). Anal. (%): Calcd for $C_{21}H_{16}N_2O$ (326.11): C, 77.29; H, 4.32; N, 8.58. Found: C, 77.25; H, 4.26; N, 8.49.

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طريقة فعالة لتشييد مشتقات البيرميدينون والبيرميدينثيون الواعدة بيولوجيا" عن طريق تفاعل ثلاث مكونات في خطوة واحدة باستخدام حفاز رابع كلوريد السيليكون

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تم تشييد سلسلة من مشتقات البيرميدينون والبيرميدينثيون بناتج نهائي عالي النسبة عند درجة حرارة الغرفة وذلك عن طريق تفاعل بجينيلي المعدل، تم الحصول على النواتج بتفاعل ثلاث مكونات في خطوة واحدة من مركبات بيتا داي كيتون، الألدهيدات و اليوريا أو الثيو يوريا في وجود كمية من حفاز رابع كلوريد السيليكون. وبعمل استكشاف لمدى تأثير نوع الحفاز ونوع المذيب ونسب المتفاعلات وجد أن أفضل نتائج تم الحصول عليها في وجود حفاز رابع كلوريد السليكون و داي كلورو ميثان كمذيب عند درجة حرارة الغرفة.