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$ZrCl_4$ or $ZrOCl_2$ under neat conditions: optimized green alternatives for the Biginelli reaction

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Abstract—Biginelli reactions were performed using either $ZrCl_4$ or $ZrOCl_2{\cdot}8H_2O$ as catalysts under neat conditions. Shorter reaction time than most of the classical methods was required when $ZrCl_4$ was used. In general, 3,4-dihydropyrimidin-2(1*H*)-ones and thioxo-3,4-dihydropyrimidin-2(1*H*)-ones were obtained under neat conditions in moderate to good yields and good purity without using harmful solvents in the work up.

The Biginelli synthesis (Fig. 1) is an easy and useful multicomponent reaction which involves the condensation between α,β-ketoesters, aldehydes and ureas or thioureas in the presence of either Lewis or mineral acids, to yield 3,4-dihydropyrimidin-2(1*H*)-ones or thioxo-3,4-dihydropyrimidin-2(1*H*)-ones.[1,2]

These compounds have been becoming very interesting due to their wide spectra of biological activities[3] and used as a starting point to prepare complex heterocyclic scaffolds with pharmacological properties.[4] These reasons have motivated researchers to extend the scope of the method to other 1,3-dicarbonyl compounds such as β-diamides,[5] cyclic diketones[6] and β-ketolactones.[7]

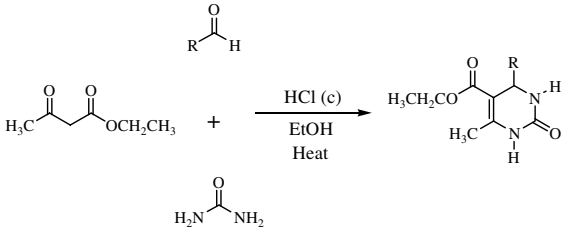

Figure 1. Classic Biginelli synthesis.

Another modification is focused on the use of different acidic catalysts mostly in the presence of a polar solvent. In that sense H_2SO_4,[8] $BF_3{\cdot}Et_2O/CuCl$,[9] $LaCl_3{\cdot}7H_2O$ with catalytic concentrated HCl,[10] $CeCl_3{\cdot}7H_2O$,[11] $InCl_3$,[12] heteropolyacids,[13] $BiCl_3$,[14] $Cu(OTf)_2$,[15] TMSCl,[16] $LiClO_4$,[17] LiBr,[18] $InBr_3$,[19] phenylpyruvic acid,[6a] $FeCl_3{\cdot}6H_2O/HCl$[20] and TMSI[21] have been employed with success but solvents such as ethanol, acetic acid, tetrahydrofuran, acetonitrile or *N*,*N*-dimethylformamide are often utilized.

In the attempt of performing reactions under green conditions other catalysts have been tested; that is the case of ytterbium derivatives under solventless conditions, but long reaction times are required (between 7 h and 48 h) and ethyl acetate and amberlyst are incorporated to the reactions work up.[22]

$ZrOCl_2{\cdot}8H_2O$ has been useful to prepare polysubstituted cyclopentenones from ketones and aldehydes,[23] homoallylic amines,[24] coumarines,[25] among others[26,27] while $ZrCl_4$ has been present in the preparation of polysubstituted cyclopentenones,[23] coumarines,[28] acetals[29] and thioacetals.[30] Both catalysts have already been tested in the Biginelli reaction. In the case of $ZrCl_4$ the reaction is performed in ethanolic media, 10% of catalyst is charged with reaction time between 4 h and 6 h and mostly urea derivatives were prepared.[31]

On the other hand, when zirconyl chloride is charged, neat conditions were set, but different mixtures of

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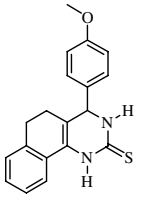
Table 1. $ZrCl_4$ was used as a catalyst (X = S)

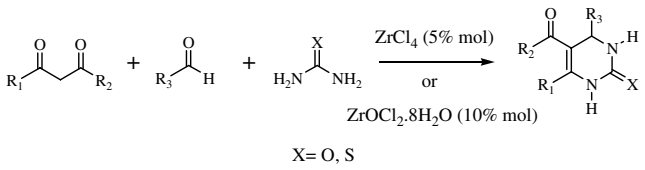
Entry	Compound	R_1	R_2	R_3	*t* (min)	Yield (%)	Mp_{Obt} (°C)/$mp_{lit.}$ (°C)
I	**1**	Me	Me	4-MeOPh	15	89.2[a]	161–163/183–184[35]
II	**2**	Me	Me	2-Cl-5-NO_2Ph	15	75.3[a]	187–190/—
III	**3**	Me	Me	3-ClPh	15	94.7[a]	243–245/—
IV	**4**	Me	Me	2-Naphtyl	15	82.5[b]	238–240/—
V	**5**	Me	Me	4-ClPh	15	90.5[c]	208/189–191 (from 2-propanol)[36]
VI	**6**	Me	Me	Ph	15	89.5[b]	214–215/220–221 (from AcOEt/Hex.)[37]
VII	**7**	Me	OEt	2-Naphtyl	15	54.7[b]	188–190/180[38]
VIII	**8**	Me	OEt	Ph	15	70.8[c]	206–207/206–207[21,35]
IX	**9**	Me	OEt	4-ClPh	15	65.5[d]	189–191/192–194 (methanol)[39]
X	**10**				30	43.8[b]	196–199/220–222[40]

Milliliters of ethanol/water used in the work up by mL of α,β-dicarbonyl compound: [a]1:5; [b]1:10; [c]1:20; [d]0:10.

harmful solvents have been employed in order to obtain products with adequate purity.[32]

In our work, only 5% of $ZrCl_4$ as a catalyst was added and the reaction time was considerably reduced as a consequence (Table 1). Only thioxo-3,4-dihydropyrimidin-2(1*H*)-ones were synthesized in order to show the enforceability of the method.

Reactions (with both catalysts) were carried out at 90–100 °C under neat conditions (Scheme 1), enhancing the catalytic power of these zirconia Lewis acids. Moreover, the referred harmful organic solvents used in zirconyl chloride reactions were replaced either by water or mixtures of ethanol/water allowing to obtain the products with good purity (Tables 1 and 2). Longer reaction times were required when lower quantities of catalysts were used.



Scheme 1.

In general, the products were obtained in good yields with an environmental friendly process. Either known or new compounds were adequately characterized. Physical and spectral data of known compounds are in good agreement with those reported in the literature. Spectral data of new compounds are shown.[33,34] Scope of the methods is well demonstrated by the synthesis of a wide range of products.

Table 2. $ZrOCl_2{\cdot}8H_2O$ was used as a catalyst

Entry	Compound	R_1	R_2	R_3	X	*t* (min)	Yield (%)	Mp_{Obt} (°C)/$mp_{lit.}$ (°C)
I	**3**	Me	Me	3-ClPh	S	180	89[a]	243–245/see comp. **3** in Table 1
II	**5**	Me	Me	4-ClPh	S	60	77[b]	208/189–191 (from 2-propanol)[36]
III	**6**	Me	Me	Ph	S	60	83[b]	214–215/220–221 (from AcOEt:Hex.)[37]
IV	**7**	Me	OEt	2-Naphthyl	S	60	72[c]	188–190/180[38]
V	**8**	Me	OEt	Ph	S	120	56[d]	206–207/206–207[21,35]
VI	**9**	Me	OEt	4-ClPh	S	130	61[e]	189–191/192–194 (from methanol)[39]
VII	**11**	Me	OEt	Ph	O	120	91.1[d]	205–206/207–208 (from ethanol)[41]
VIII	**12**	Me	OEt	3-ClPh	S	120	60.1[f]	192–196/not reported[42]
IX	**13**	Me	OEt	4-MeOPh	S	120	66.9[f]	154–155/150–152 (from methanol)[43]
X	**14**	Me	OEt	2-ClPh	S	120	40.7[f]	168–169/168[44]
XI	**15**	Me	OEt	4-ClPh	O	120	42.5[f]	210–211/210–212[22a]
XII	**16**	Me	OEt	3,4-MeOPh	S	120	52[f]	165–166/173[45]
XIII	**17**	Me	Me	3-ClPh	O	30	93.1[a]	229–231/284–285[46]
XIV	**18**	Me	Me	2-ClPh	S	180	90.1[a]	173–174/—
XV	**19**	Me	Me	2-ClPh	O	30	99.7[a]	228–230/257–258[46]
XVI	**20**	Ph	OEt	Ph	S	90	85.6[c]	183–185/192[47]
XVII	**21**	Ph	OEt	4-MeOPh	S	180	88.8[d]	151–152/not reported[48]
XVIII	**22**	Ph	OEt	2-Cl-5-NO_2Ph	S	30	88.3[d]	239/—

Milliliters of ethanol/water used in the work up by mL of α,β-dicarbonyl compound: [a]0:20; [b]0:15; [c]2:10; [d]1:5, [e]1:15; [f]8:8.

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33. General procedure when $ZrCl_4$ is used: Urea or thiourea (1.3 mmol) was added to a mixture of α,β-dicarbonyl compound (1 mmol) (or cyclic ketone, see entry **X** in Table 1) and aldehyde (1 mmol), left at 90–100°C; then $ZrCl_4$ (5% mol) was added and left with good stirring at the same temperature for the referred time (see Table 1). To the obtained solid was added ethanol (see Table 1) and left to stir at room temperature until the mixture becomes homogeneous. Water is slowly added (see Table 1) and left to stir at room temperature for 1 h. The precipitate was filtered and washed with a similar quantity of a mixture of ethanol/water (see Table 1) and dried at 60 °C until constant weight.
1-[4-(2-Chloro-5-nitrophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydro-5-pyrimidinyl]ethanone (**2**): ^{1}H NMR (DMSO-d_6): δ 10.48 (s, 1H, NH); 9.78 (s, 1H, NH); 8.11 (dd, 1H, H-Ph); 7.95 (d, $J = 2.52$ Hz, 1H, H-Ph); 7.74 (d, $J = 8.85$ Hz, 1H, H-Ph); 5.71 (d, $J = 3.30$ Hz, 1H, H-4); 2.39 (s, 3H, CH_3); 2.17 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6): δ 194.32, 174.09, 146.70, 145.44, 141.67, 138.85, 131.30, 124.17, 123.62, 109.67, 51.86, 30.67, 18.28. Elem. Anal. Calcd: C, 47.93; H, 3.71; Cl, 10.88; N, 12.90; O, 14.73; S, 9.84. Found: C, 47.88; H, 3.65; Cl, 10.93; N, 12.95; O, 14.80; S, 9.79.
1-[4-(3-Chlorophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydro-5-pyrimidinyl]ethanone (**3**): ^{1}H NMR (DMSO-d_6): δ 10.36 (s, 1H, NH); 9.79 (s, 1H, NH); 7.43–7.37 (m, 2H, H-Ph); 7.24 (d, $J = 1.7$ Hz, H, H-Ph); 7.18–7.14 (m, 2H, H-Ph); 5.28 (d, $J = 3.85$ Hz, H-4); 2.42 (s, 3H, CH_3); 2.23 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6): δ 194.63, 174.30, 145.19, 145.14, 133.13, 130.59, 127.61, 126.35, 125.04, 110.20, 53.06, 30.55, 18.31. Elem. Anal. Calcd: C, 55.61; H, 4.67; Cl, 12.63; N, 9.98; O, 5.70; S, 11.42. Found: C, 55.70; H, 4.73; Cl, 12.60; N, 10.01; O, 5.56; S, 11.40.
1-[6-Methyl-4-(2-naphthyl)-2-thioxo-1,2,3,4-tetrahydro-5-pyrimidinyl]ethanone (**4**): ^{1}H NMR (DMSO-d_6): δ 10.36 (s, 1H); 9.89 (s, 1H, NH); 7.94–7.88 (m, 3H, H-Ph); 7.75 (s, 1H, H-Ph); 7.53–7.44 (m, 3H, H-Ph); 5.49 (d, $J = 3.25$ Hz, 1H); 2.40 (s, 3H); 2.20 (s, 3H). ^{13}C NMR (DMSO-d_6): δ 194.81, 174.07, 144.72, 140.19, 132.41, 132.23, 128.55, 127.89, 127.45, 126.35, 126.13, 124.98, 124.91, 110.18, 54.03, 30.39, 18.29. Elem. Anal. Calcd: C, 68.89; H, 5.44; N, 9.45; O, 5.40; S, 10.82. Found: C, 68.92; H, 5.40; N, 9.48; O, 5.35; S, 10.85.
34. General procedure when $ZrOCl_2{\cdot}8H_2O$ is used: Reactions were carried out in the same way as for $ZrCl_4$. In this case 10 mol % of $ZrOCl_2{\cdot}8H_2O$ was used. Quantities of ethanol/water mixtures are referred in Table 2.
1-[4-(2-Chlorophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydro-5-pyrimidinyl]ethanone (**18**): ^{1}H NMR (DMSO-d_6): δ 10.36 (s, 1H, NH); 9.65 (d, $J = 2.5$ Hz, 1H, NH); 7.48–7.44 (m, 1H, H-Ph); 7.35–7.31 (m, 2H, H-Ph); 7.27–7.26 (m, 1H, H-Ph); 5.70 (d, $J = 5$ Hz, 1H, H-4); 2.38 (s, 3H, CH_3); 2.12 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6): δ 194.53, 173.88, 144.86, 139.69, 131.83, 129.86, 129.06, 127.89, 109.68, 51.55, 30.25, 18.15. Elem. Anal. Calcd: C, 55.61; H, 4.67; Cl, 12.63; N, 9.98; O, 5.70; S, 11.42. Found: C, 55.64; H, 4.70; Cl, 12.60; N, 10.02; O, 5.59; S, 11.45.
Ethyl 4-(2-chloro-5-nitrophenyl)-6-phenyl-2-thioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate (**22**): ^{1}H NMR (DMSO-d_6): δ 10.74 (s, 1H, NH), 9.83 (d, $J = 1.75$ Hz,

1H, NH); 8.29 (d, $J = 2.5$ Hz, 1H, H-Ph); 8.22 (dd, 1H, H-Ph); 7.84 (d, $J = 7.5$ Hz, 1H, H-Ph); 7.47–7.37 (m, 5H, H-Ph); 5.84 (d, $J = 2.5$ Hz, 1H, H-4); 3.70 (dd, 2H, CH_2); 0.71 (t, 3H, CH_3). ^{13}C NMR (DMSO-d_6): δ 174.23, 164.13, 146.72, 146.62, 141.64, 138.96, 133.63, 131.47, 129.20, 128.32, 127.80, 124.36, 124.27, 99.86, 59.51, 52.45, 13.19. Elem. Anal. Calcd: C, 54.61; H, 3.86; Cl, 8.48; N, 10.06; O, 15.32; S, 7.67. Found: C, 54.64; H, 3.83; Cl, 8.50; N, 10.09; O, 15.29; S, 7.65.

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