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On the regioselectivity in the reaction of aliphatic ketones and aromatic nitriles. Regiospecific synthesis of alkylarylpyrimidines

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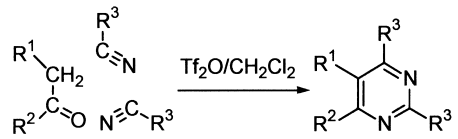
Abstract—The reaction of aliphatic ketones with aliphatic or aromatic nitriles in the presence of trifluoromethanesulfonic anhydride has been shown to be a very useful method for the preparation of alkyl- and aryl-pirimidines. The reaction shows a high degree of regioselectivity that depends on the characteristics of the residues attached at the carbonyl group. The results from different branched symmetric and asymmetric ketones are shown. Molecular mechanics calculations permit an explanation and predict the results obtained. Regiospecific synthesis of alkyl aryl pyrimidines is described.

1. Introduction

One of the more important groups of heterocyclic compounds are pyrimidines, because they are components of naturally occurring products present in a large number of biological processes.[1,2] The alkyl and arylpyrimidines are a interesting class of compounds which have found applications as herbicides,[3] insecticides[4] and liquid crystal chemistry.[5] Arylpyrimidines present also activity as selective modulators of CRF receptors.[6] Alkylpyrimidines are also interesting as non-nucleophilic bases in glycosylation and other reactions.[7,8] (Scheme 1).



Scheme 1.

The cyclization of ketones with nitriles in the presence of triflic anhydride, Tf_2O, $[(CF_3SO_2)_2O]$ has been shown to be a very useful reaction for the preparation of pyrimidines.[9] The extension of this procedure has enabled the synthesis of several types of heterocyclic compounds, such as bicyclic pyrimidines and isoquinolines.[10] More detailed applications of this reaction are found in Ref. 13 and in references cited herein.

The proposed general mechanism[9] permits a good explanation of the nature of the different classes of compounds formed.[10–12] However, the question regarding to the driving force which explains the selectivity in the obtained alkylpyrimidines **3** and/or **4** (Scheme 3), from branched aliphatic ketones **1** as well as their mechanistic implications demands a additional clarified answer. We wish to report here a study of the reaction of branched symmetric and asymmetric aliphatic ketones **1** with a variety of electron demanding aromatic nitriles **2** in the presence of triflic anhydride, whereby isomeric pyrimidines **3** and/or **4** could be formed. The reaction is carried out into different 2- and 3-ketones (entries **1a–i**, **1j–r**). We have used the system number indicated in Scheme 3 to enable an easier discussion of the results.

2. Results and discussion

Pyrimidines **3** and/or **4** were prepared in good yield following the general procedure[13] from ketones **1** and aryl nitriles **2** in the presence of triflic anhydride. The results obtained (Scheme 3) show that the reaction takes place with a high regioselectivity in the formation of the products. Thus, from 2-ketones (R^1=H) 4-methylpyrimidines **3** were regiospecifically obtained (entries **a–i**). From 3-ketones (R^1=CH_3), the regioselectivity depends on the length of the alkyl residue R^2 attached at the carbonyl group. When R^2=CH_2CH_3, different ratios of pyrimidines **3/4** were obtained, whereby a high regioselectivity towards 5-methylpyrimidines **4** was observed. 5-Methylpyrimidines **4** were regiospecifically obtained (entries **n–r**) when R^2= Pr, Bu. Only for R^3=C_6H_5 (entry **m**), was a small amount of 4-ethylpyrimidine **3** obtained (Scheme 2).

Keywords: aliphatic ketones; regioselectivity; alkylarylpyrimidines.
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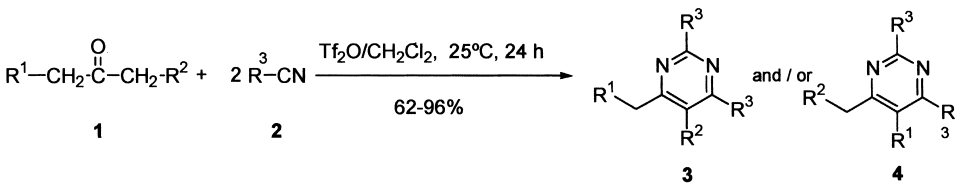
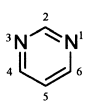
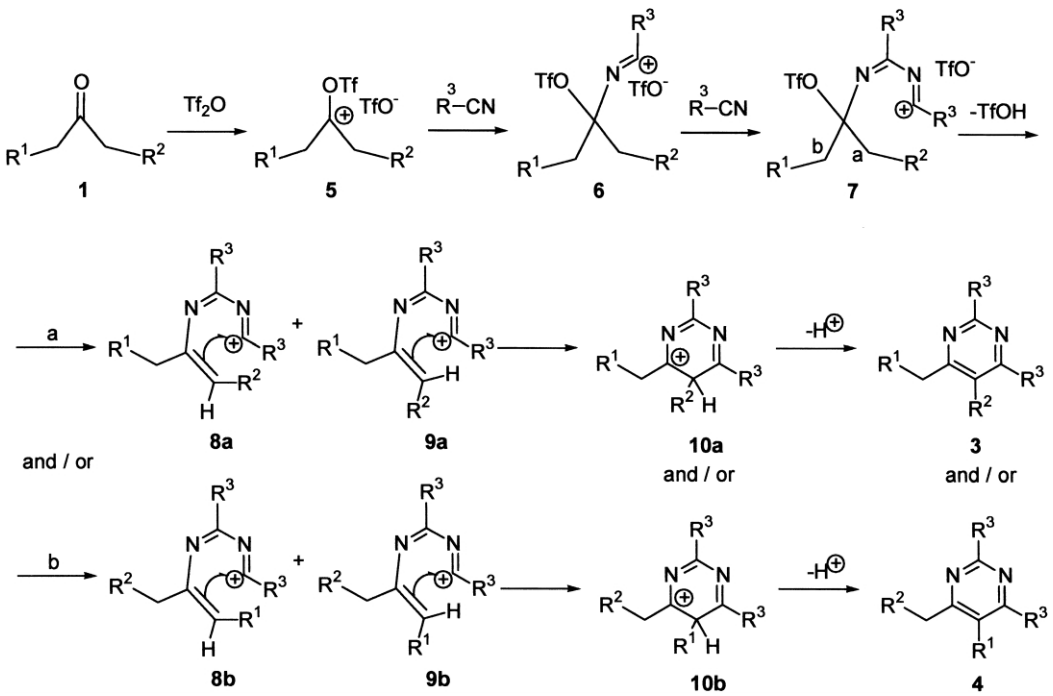


1	2	3+4(%)*	3/4**
a; R^1 = H; R^2 = CH_2CH_3	R^3 = C_6H_5	80	100/0
b; R^1 = H; R^2 = CH_2CH_3	R^3 = $pCH_3C_6H_4$	54	100/0
c; R^1 = H; R^2 = CH_2CH_3	R^3 = $pClC_6H_4$	80	100/0
d; R^1 = H; R^2 = $(CH_2)_2CH_3$	R^3 = C_6H_5	93	100/0
e; R^1 = H; R^2 = $(CH_2)_2CH_3$	R^3 = $pCH_3C_6H_4$	80	100/0
f; R^1 = H; R^2 = $(CH_2)_2CH_3$	R^3 = $pClC_6H_4$	69	100/0
g; R^1 = H; R^2 = $(CH_2)_3CH_3$	R^3 = C_6H_5	93	100/0
h; R^1 = H; R^2 = $(CH_2)_3CH_3$	R^3 = $pCH_3C_6H_4$	83	100/0
i; R^1 = H; R^2 = $(CH_2)_3CH_3$	R^3 = $pClC_6H_4$	60	100/0
j; R^1 = CH_3; R^2 = CH_2 CH_3	R^3 = C_6H_5	74	19/81
k; R^1 = CH_3; R^2 = CH_2CH_3	R^3 = $pCH_3C_6H_4$	89	26/74
l; R^1 = CH_3; R^2 = CH_2CH_3	R^3 = $pClC_6H_4$	86	35/65
m; R^1 = CH_3; R^2 = $(CH_2)_2CH_3$	R^3 = C_6H_5	89	5/95
n; R^1 = CH_3; R^2 = $(CH_2)_2CH_3$	R^3 = $pCH_3C_6H_4$	93	0/100
o; R^1 = CH_3; R^2 = $(CH_2)_2CH_3$	R^3 = $pClC_6H_4$	67	0/100
p; R^1 = CH_3; R^2 = $(CH_2)_3CH_3$	R^3 = C_6H_5	87	0/100
q; R^1 = CH_3; R^2 = $(CH_2)_3CH_3$	R^3 = $pCH_3C_6H_4$	96	0/100
r; R^1 = CH_3; R^2 = $(CH_2)_3CH_3$	R^3 = $pClC_6H_4$	93	0/100

* isolated product
**determined by ^{1}H-NMR



Scheme 2.



Scheme 3.

These results show that the selectivity of the process is completely controlled by small variations in the alkyl groups attached to the carbonyl group. A more detailed observation of the general mechanism[14] for the synthesis of pyrimidines from alkyl ketones and triflic anhydride (Scheme 3), could explain the above mentioned results. The reaction starts with the electrophilic attack of triflic anhydride on the carbonyl compound **1** and the formation of a (trifluoromethanesulfonyl)carbenium ion **5**. The efficient nucleophilic trapping of **5** leads prior **6** to the imonium intermediate **7**. The elimination of triflic acid from **7** will take place easily since the triflate anion is a excellent leaving group[15] and could be performed through two different possibilities **a** and **b**. The elimination leads to the stable conjugated *E*/*Z* olefinic intermediates **8** and **9**, respectively, which corresponds to the reaction paths **a** and/or **b**. Both of them lead to the same pyrimidine **3** or **4** The nature and ratio of **3** and/or **4** formed after cyclization (intermediates **10a** and/or **10b**) and final lost of a proton, should hence depend mainly on the relative stabilities of the intermediates **8** and **9**.

According to this hypothesis, we have studied their relative stability by means of molecular mechanics (AM1) within Hyperchem v6.03 program. In Table 1 are listed the values of the heat of formation (kcal/mol) corresponding to the species **8a**,**9a** and **8b**,**9b** and their differences $\Delta H_{f_{8a,9a}} - \Delta H_{f_{8b,9b}}$ ($\Delta\Delta H_f$).

The regioselectivity of the process and the ratio of the obtained pyrimidines **3** and/or **4** correlate very well with the values of the differences $\Delta\Delta H_f$ found. The main product will be that corresponding to the more stable intermediate **8** and/or **9**. Higher selectivities are observed when greater values of the difference $\Delta\Delta H_f$ occur. In this regard, for values up to 1.2 kcal/mol both pyrimidines **3/4** are obtained (entries **j**–**m**), whereby **4** predominates as corresponds to the more stable intermediate **8b**,**9b**. Pyrimidines **3** (entries **a**–**i**) and **4** (entries **n**–**r**) were regiospecifically obtained for values of $\Delta\Delta H_f$ greater than 1.2 kcal/mol. Positive values of $\Delta\Delta H_f$ permit to explain the formation of pyrimidines **4** as single product, while negative ones explain the isolation of pyrimidines **3**.

Table 1. Values of the heat of formation of intermediates **8** and **9**

Entry	$H_{f_{8a,9a}}$	$H_{f_{8b,9b}}$	$\Delta H_{f_{8a,9a}} - \Delta H_{f_{8b,9b}}$ ($\Delta\Delta H_f$, kcal/mol)	**3/4** (%)
a	−129.1	−124.9	−4.2	100/0
b	−129.1	−140.6	−5.1	100/0
c	−141.5	−136.2	−5.3	100/0
d	−136.0	−132.0	−4.0	100/0
e	−152.3	−147.4	−4.9	100/0
f	−148.0	−144.2	−3.8	100/0
g	−142.7	−138.9	−3.8	100/0
h	−153.3	−148.7	−4.5	100/0
i	−154.9	−151.0	−3.9	100/0
j	−134.0	−135.1	1.1	19/81
k	−149.9	−150.9	1.0	26/74
l	−146.2	−147.1	0.9	35/65
m	−139.9	−141.1	1.2	5/95
n	−155.2	−157.3	2.1	0/100
o	−152.0	−153.9	1.9	0/100
p	−146.4	−148.0	1.6	0/100
q	−161.1	−164.5	3.4	0/100
r	−157.8	−160.9	3.1	0/100

We can conclude that these results permit the clarification of the mechanism of the reaction of ketones and nitriles regarding a rational explanation for the regioselectivity found. Derived from these findings, a regiospecific synthesis of alkyl aryl pyrimidines is reported.

3. Experimental

All reagents were commercial grade and were used as received unless otherwise indicated. Triflic anhydride was prepared from TfOH and redistilled twice prior to use. Melting points were determined on a Gallenkamp apparatus and are uncorrected. NMR spectra were taken on a Bruker DPX 300 and Varian VXR at 300 MHz for ^{1}H and 75.47 MHz for ^{13}C. Chemical shifts (δ_H and δ_C) are given to residual $CHCl_3$ (7.26 and 77.0 ppm, respectively). *J* values are in Hertz. Infrared spectra were taken on a Shimadzu FTIR 8300. Mass spectra were carried out on a HP 5989A quadrupole instrument at 70 eV with a source temperature of 250°C. Elemental analyses: Perkin–Elmer 2400 CHN. TLC analyses were performed on silica gel $60F_{250}$ plates and column chromatography was carried out on silica gel 60 (70–230 mesh). Reaction solvents were distilled from appropriate drying agent before use.

3.1. Preparation of 4,5-dialkyl-2,6-diaryl pyrimidines 3 and/or 4: general procedure

A solution of Tf_2O (2.01 g, 7.13 mmol) in $CHCl_3$ (15 mL) was added dropwise to a stirred solution of ketone (6 mmol) and nitrile **4** (6.85 mmol) in CH_2Cl_2 (10 mL) at room temperature. The formation of pyrimidines can be monitored by TLC. The reaction mixture was hydrolysed by careful addition of saturated aqueous solution of sodium hydrogen carbonate until it was basic. The organic layer was separated, washed with brine, dried ($MgSO_4$), and the solvent eliminated under reduced pressure. The crude product was purified by column chromatography using hexane/ethyl acetate 7:3 as eluent. The corresponding pyrimidines were distilled or recrystallized.

3.1.1. 5-Ethyl-4-methyl-2,6-diphenyl-pyrimidine 3a. Reaction time: 24 h. Purification of crude product by recrystallization affords 1.1 g (80%) of title compound as white solid, p.f. 123–125°C (EtOH); ν (KBr): 3057, 2935, 1541, 1390, 1070, 1026, 761, 698 cm^1; δ_H ($CDCl_3$): 1.17 (t, 3H, *J*=7.6 Hz, CH_3), 2.68 (s, 3H, CH_3), 2.72 (2H, c, *J*=7.6 Hz, CH_2), 7.47 (m, 6H, arom), 7.56, 8.48 (m, 4H, arom) ppm; δ_C ($CDCl_3$): 14.00, 22.28 (CH_3), 21.28 (CH_2), 127.95, 128.11, 128.24, 128.47, 128.51, 129.90, 130.02, 137.93, 139.30, 161.02, 165.40, 166.24 (C arom) ppm; *m*/*z* (EI, 70 eV): 274 ($M^{+\cdot}$, 71), 273 ($M^{+\cdot}-1$, 100), 259 ($M^{+\cdot}-CH_3^{\cdot}$, 12), 77 ($C_6H_5^+$, 10); Anal. calcd for $C_{19}H_{18}N_2$, C 83.18% H 6.61% N 10.21%. Found C 84.14% H 6.01% N 10.29%.

3.1.2. 5-Ethyl-4-methyl-2,6-di-*p*-tolyl-pyrimidine 3b. Reaction time: 36 h. Purification of crude product by recrystallization affords 1.1 g (54%) of title compound as yellow solid, mp 123–125°C (EtOH); ν (KBr): 3020, 2960, 1541, 1392, 1170, 1020, 804, 725 cm^1; δ_H ($CDCl_3$): 1.14 (t, 3H, *J*=7.3 Hz, CH_3), 2.40 (s, 3H, CH_3), 2.44 (s, 3H, CH_3),

2.67 (s, 3H, CH_3), 2.72 (c, 2H, J=7.3 Hz, CH_2), 7.27 (m, 4H, arom), 7.47, 8.36 (4H, AA′XX′, 4H) ppm; δ_C ($CDCl_3$): 14.17, 21.34, 21.45, 22.40 (CH_3), 21.64 (CH_2), 127.98, 128.59, 128.89, 129.07, 129.33, 129.76, 135.38, 136.66, 140.02, 153.20, 161.14, 165.43 (C arom) ppm; *m/z* (EI, 70 eV): 302 ($M^{+\cdot}$, 74), 301 ($M^{+\cdot}-1$, 100), 287 ($M^{+\cdot}-CH_3^{\cdot}$, 17), 91 ($C_7H_7^+$, 4); Anal. calcd for $C_{21}H_{22}N_2$, C 83.40% H 7.33% N 9.26%. Found C 82.80% H 7.81% N 9.21%.

3.1.3. 2,6-Bis-(4-chloro-phenyl)-5-ethyl-4-methyl-pyrimidine 3c. Reaction time: 36 h. Purification of crude product by recrystallization affords 1.27 g (80%) of title compound as yellow solid, mp 144–145°C (EtOH); ν (KBr): 2966, 1577, 1539, 1400, 1089, 1014, 804, 744 cm^1; δ_H ($CDCl_3$): 1.13 (t, 3H, J=7.5 Hz, CH_3), 2.67 (s, 3H, CH_3), 2.70 (c, 2H, J=7.5 Hz, CH_2), 7.41 (m, 2H, arom), 7.48 (s, 4H, arom), 8.40 (m, 2H, arom) ppm; δ_C ($CDCl_3$): 13.92, 22.23 (CH_3), 21.45 (CH_2), 128.55, 128.58, 129.41, 130.06, 130.35, 134.91, 136.33, 137.64, 160.19, 164.33, 165.40, 166.77 (C arom) ppm; *m/z* (EI, 70 eV): 342 ($M^{+\cdot}$, 70), 341 ($M^{+\cdot}-1$, 100), 327 ($M^{+\cdot}-CH_3^{\cdot}$, 12), 307 ($M^{+\cdot}-Cl$, 5); Anal. calcd for $C_{19}H_{16}Cl_2N_2$, C 66.48% H 4.70% Cl 20.66% N 8.16%. Found C 66.08% H 4.95% Cl 20.16% N 8.39%.

3.1.4. 4-Methyl-2,6-diphenyl-5-propyl-pyrimidine 3d. Reaction time: 36 h. Purification of crude product by recrystallization affords 1.23 g (93%) of title compound as yellow solid, mp 65–66°C (EtOH); ν (KBr): 3421, 2956, 1541, 1392, 698 cm^1; δ_H ($CDCl_3$): 0.82 (t, 3H, J=7.3 Hz, CH_3), 1.32 (sext, 2H, J=7.3 Hz, CH_2), 1.45 (m, 2H, CH_2), 2.68 (m, 5H, CH_2, CH_3), 7.45 (m, 6H, arom), 7.55, 8.45 (m, 4H, arom) ppm; δ_C ($CDCl_3$): 13.62, 22.56 (CH_3), 22.70, 28.09, 31.81 (CH_2), 128.03, 128.19, 128.36, 128.56, 128.70, 129.03, 130.01, 138.02, 139.44, 161.07, 165.65, 166.41 (C arom) ppm; *m/z* (EI, 70 eV): 302 ($M^{+\cdot}$, 77), 301 ($M^{+\cdot}-1$, 49), 287 ($M^{+\cdot}-CH_3^{\cdot}$, 14), 273 ($C_2H_5^{\cdot}$, 100), 259 ($M^{+\cdot}-C_3H_7^{\cdot}$, 82); Anal. calcd for $C_{20}H_{20}N_2$, C 83.30% H 6.99% N 9.71%. Found C 84.14% H 6.09% N 9.98%.

3.1.5. 4-Methyl-5-propyl-2,6-di-*p*-tolyl-pyrimidine 3e. Reaction time: 36 h. Purification of crude product by recrystallization affords 1.12 g (83%) of title compound as white solid, mp 72–73°C (EtOH); ν (KBr): 3421, 2923, 1580, 1388, 1164, 1085, 850, 802 cm^1; δ_H ($CDCl_3$): 0.85 (t, 3H, J=7.3 Hz, CH_3), 1.28 (sext, 2H, J=7.3 Hz, CH_2), 1.45 (m, 2H, CH_2), 2.38, 2.43 (s, 6H, $2CH_3$), 2.65 (s, 3H, CH_3), 2.69 (m, 2H, CH_2), 7.27, 7.45 (AA′XX′, 4H), 7.55, 8.35 (AA′XX′, 4H) ppm; δ_C ($CDCl_3$): 13.62, 21.35, 21.46, 22.56 (CH_3), 22.70, 28.17, 31.88 (CH_2), 127.95, 128.66, 128.86, 129.07, 129.82, 132.05, 135.36, 136.69, 138.41, 140.01, 165.53, 166.16 (C arom) ppm; *m/z* (EI, 70 eV): 330 ($M^{+\cdot}$, 81), 329 ($M^{+\cdot}-1$, 43), 315 ($M^{+\cdot}-CH_3^{\cdot}$, 12), 301 ($M^{+\cdot}-C_2H_5^{\cdot}$, 100), 287 ($M^{+\cdot}-C_3H_7^{\cdot}$, 98), 91 ($C_7H_7^+$, 4), 52 (5); Anal. calcd for $C_{21}H_{22}N_2$, C 83.40% H 7.33% N 9.26%. Found C 82.85% H 7.85% N 8.89%.

3.1.6. 2,6-Bis-(4-chloro-phenyl)-4-methyl-5-propyl-pyrimidine 3f. Reaction time: 36 h. Purification of crude product by recrystallization affords 1.12 g (80%) of title compound as yellow solid, mp 37–40°C (EtOH); ν (KBr): 3421, 2952, 1541, 1390, 802 cm^1; δ_H ($CDCl_3$): 0.85 (t, 3H, J=7.3 Hz, CH_3), 1.28 (sext, 2H, J=7.3 Hz, CH_2), 1.43 (m, 4H, $2CH_2$), 1.67 (s, 3H, CH_3), 2.68 (m, 5H, CH_2, CH_3) 7.45 (m, 4H, arom), 7.55, 8.45 (m, 4H, arom) ppm; δ_C ($CDCl_3$): 13.64, 22.55 (CH_3), 22.72, 28.10, 31.79 (CH_2), 128.52, 128.58, 129.36, 130.11, 133.38, 134.85, 136.29, 136.31, 139.57, 160.13, 164.46, 166.81 (C arom) ppm; *m/z* (EI, 70 eV): 370 ($M^{+\cdot}$, 78), 369 ($M^{+\cdot}-1$, 29), 355 ($M^{+\cdot}-CH_3^{\cdot}$, 9), 341 ($M^{+\cdot}-C_2H_5^{\cdot}$, 13), 327 ($M^{+\cdot}-C_3H_7^{\cdot}$, 100); Anal. calcd for $C_{19}H_{16}Cl_2N_2$, C 66.48% H 4.70% Cl 20.66% N 8.16%. Found C 67.44% H 5.01% Cl 20.12% N 8.82%.

3.1.7. 5-Butyl-4-methyl-2,6-diphenyl-pyrimidine 3g. Reaction time: 36 h. Purification of crude product by recrystallization affords 1.23 g (93%) of title compound as yellow solid, mp 61–62°C (MeOH); ν (KBr): 2920, 1541, 1494, 1390, 1024, 761, 694 cm^1; δ_H ($CDCl_3$): 0.85 (m, 3H, CH_3), 1.20 (m, 4H, $2CH_2$), 1.50 (m, 2H, CH_2), 2.70 (m, 5H, CH_2, CH_3), 7.50 (m, 8H, arom), 8.50 (m, 2H, arom) ppm; δ_C ($CDCl_3$): 13.88, 22.11 (CH_3), 22.58, 28.34, 29.33, 31.77 (CH_2), 128.03, 128.20, 128.36, 128.56, 128.68, 129.07, 130.01, 136.92, 138.02, 161.06, 165.64, 166.40 (C arom) ppm; *m/z* (EI, 70 eV): 316 ($M^{+\cdot}$, 83), 315 ($M^{+\cdot}-1$, 49), 301 ($M^{+\cdot}-CH_3^{\cdot}$, 99), 287 ($M^{+\cdot}-C_2H_5^{\cdot}$, 10), 277 ($M^{+\cdot}-C_3H_7^{\cdot}$, 99), 259 ($M^{+\cdot}-C_4H_9^{\cdot}$, 100), 77 ($C_6H_5^+$,6), Anal. calcd for $C_{21}H_{22}N_2$, C 83.40% H 7.33% N 9.26%. Found C 81.51% H 7.92% N 9.92%.

3.1.8. 5-Butyl-4-methyl-2,6-di-*p*-tolyl-pyrimidine 3h. Reaction time: 36 h. Purification of crude product by recrystallization affords 1.12 g (83%) of title compound as yellow solid, mp 55–56°C (MeOH); ν (KBr): 2925, 1541, 1390, 802 cm^1; δ_H ($CDCl_3$): 0.83 (m, 3H, CH_3), 1.25 (m, 4H, $2CH_2$), 1.44 (m, 2H, CH_2), 2.40 (s, 3H, CH_3), 2.43 (s, 3H, 3H), 2.65 (s, 3H, CH_3), 2.70 (m, 2H, CH_2), 7.24 (m, 4H, arom), 7.45, 8.33 (AA′XX′, 4H) ppm; δ_C ($CDCl_3$): 13.91, 21.35, 21.45 (CH_3), 22.17 (CH_2), 22.57 (CH_3), 28.41, 29.40, 31.81 (CH_2), 109.95, 127.34, 127.95, 128.64, 128.86, 129.07, 136.89, 140.01, 159.40, 163.23, 166.16 (C arom) ppm; *m/z* (EI, 70 eV): 344 ($M^{+\cdot}$, 87), 343 ($M^{+\cdot}-1$, 44), 329 ($M^{+\cdot}-CH_3^{\cdot}$, 23), 315 ($M^{+\cdot}-C_2H_5^{\cdot}$, 8), 301 ($M^{+\cdot}-C_3H_7^{\cdot}$, 82), 287 ($M^{+\cdot}-C_4H_9^{\cdot}$, 100); Anal. calcd for $C_{23}H_{26}N_2$, C 83.59% H 7.93% N 8.48%. Found C 82.79% H 8.53% N 8.96%.

3.1.9. 5-Butyl-2,6-bis-(4-chloro-phenyl)-4-methyl-pyrimidine 3i. Reaction time: 24 h. Purification of crude product by recrystallization affords 0.9 g (60%) of title compound as yellow solid, mp 101–102°C (EtOH); ν (KBr): 2920, 1595, 1539, 1400, 1085, 1014, 804, 725 cm^1; δ_H ($CDCl_3$): 0.85 (m, 3H, CH_3), 1.23 (m, 4H, $2CH_2$), 1.45 (m, 2H, CH_2), 2.66 (m, 5H, CH_2, CH_3), 7.41 (m, 2H, arom), 7.48 (s, 4H, arom), 8.40 (m, 2H, arom) ppm; δ_C ($CDCl_3$): 13.88 (CH_3), 22.15 (CH_2), 22.58 (CH_3), 28.34, 29.35, 31.77 (CH_2), 128.52, 128.58, 129.28, 129.37, 130.09, 134.86, 136.31, 136.85, 137.69, 160.13, 164.46, 166.85 (C arom) ppm; *m/z* (EI, 70 eV): 384 ($M^{+\cdot}$, 61), 383 ($M^{+\cdot}-1$, 21), 369 ($M^{+\cdot}-CH_3^{\cdot}$, 15), 355 ($M^{+\cdot}-C_2H_5^{\cdot}$, 6), 341 ($M^{+\cdot}-C_3H_7^{\cdot}$, 38), 327 ($M^{+\cdot}-C_4H_9^{\cdot}$, 100); Anal. calcd for $C_{21}H_{20}Cl_2N_2$, C 67.93% H 5.43% Cl 19.10% N 7.54%. Found C 69.43% H 5.01% Cl 19.73% N 6.93%.

3.1.10. 4,5-Diethyl-2,6-diphenyl-pyrimidine 3j and 5-methyl-4-propyl-2,6-diphenyl-pyrimidine 4j. Reaction time: 36 h. Purification of crude product by recrystallization

affords 0.6 g (74%) of a mixture of compounds **3j** and **4j** as white solid, mp 55–57°C (MeOH). The ratio of **3j/4j** (19:81) was determined by ^{1}H NMR); *m/z* (EI, 70 eV): 288 ($M^{+\cdot}$, 53).

3.1.11. 4,5-Diethyl-2,6-di-*p*-tolyl-pyrimidine 3k and 5-methyl-4-propyl-2,6-di-*p*-tolyl-pyrimidine 4k. Reaction time: 36 h. Purification of crude product by recrystallization affords 1.33 g (89%) of a mixture of compounds as pale yellow solid, mp 76–77°C (MeOH). The ratio of **3k/4k** (26:74) was determined by ^{1}H NMR); *m/z* (EI, 70 eV): 315 ($M^{+\cdot}$, 100).

3.1.12. 4,5-Diethyl-2,6-bis-(4-chloro-phenyl)-pyrimidine 3l and 5-methyl-4-propyl-2,6-bis-(4-chloro-phenyl)-pyrimidine 4l. Reaction time: 12 h. Purification of crude product by recrystallization affords 1.84 g (86%) of a mixture of compounds as white solid, mp 107–108°C (MeOH). The ratio of **3j/4j** (19:81) was determined by ^{1}H NMR); *m/z* (EI, 70 eV): 355 ($M^{+\cdot}$, 100).

3.1.13. 4-Ethyl-2,6-diphenyl-5-propyl-pyrimidine 3m and 4-butyl-5-methyl-pyrimidine 4m. Reaction time: 36 h. Purification of crude product by recrystallization affords 0.6 g (45%) of a mixture of compounds **3m** and **4m** as pale yellow solid, mp 55–57°C (MeOH). The ratio of **3k/4k** (5:95) was determined by ^{1}H NMR); *m/z* (EI, 70 eV): 302 ($M^{+\cdot}$, 100).

3.1.14. 4-Butyl-5-methyl-2,6-di-*p*-tolyl-pyrimidine 4n. Reaction time: 12 h. Purification of crude product by recrystallization affords 0.72 g (50%) of title compound as yellow solid, mp 91–92°C (MeOH); ν (KBr): 2940, 1540, 1400, 1380, 800 cm^1; δ_H ($CDCl_3$): 1.01 (t, 3H, J=7.3 Hz, CH_3), 1.51 (sext, 2H, J=7.3 Hz, CH_2), 1.84 (q, 2H, J=7.3 Hz, CH_2), 2.33 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 2.88 (t, 2H, J=7.3 Hz, CH_2), 7.27 (m, 4H, arom), 7.58, 8.39 (m, 4H, arom) ppm; δ_C ($CDCl_3$): 14.07, 15.07 (CH_3), 22.60, 27.45, 31.82, 35.43 (CH_2), 123.46, 128.48, 128.54, 129.36, 129.69, 130.66, 133.38, 136.21, 136.55, 160.58, 163.97, 170.38 (C arom) ppm; *m/z* (EI, 70 eV): 330 ($M^{+\cdot}$, 13), 329 ($M^{+\cdot}-1$, 16), 315 ($M^{+\cdot}-CH_3^{\cdot}$, 11), 301 ($M^{+\cdot}-C_2H_5^{\cdot}$, 13), 287 ($M^{+\cdot}-C_3H_7^{\cdot}$, 100), 273 ($M^{+\cdot}-C_4H_9^{\cdot}$, 11), 91 ($C_7H_7^+$, 5); Anal. calcd for $C_{23}H_{26}N_2$, C 83.59% H 7.93% N 8.48%. Found C 84.63% H 7.06% N 8.94%.

3.1.15. 4-Butyl-5-methyl-2,6-bis-(4-chloro-phenyl)-pyrimidine 4o. Reaction time: 24 h. Purification of crude product by recrystallization affords 1.09 g (67%) of title compound as yellow solid, mp 119–120°C (MeOH); ν (KBr): 2960, 1600, 1540, 1400, 1100, 1020, 850, 800 cm^1; δ_H ($CDCl_3$): 1.02 (t, 3H, J=7.3 Hz, CH_3), 1.51 (sext, 2H, J=7.3 Hz, CH_2), 1.84 (q, 2H, J=7.3 Hz, CH_2), 2.33 (s, 3H, CH_3), 2.88 (t, 2H, J=7.3 Hz, CH_2), 7.45 (d, 4H, J=8.4 Hz, arom), 7.57 (d, 2H, J=8.4 Hz, arom), 8.44 (d, 4H, J=8.4 Hz, arom) ppm; δ_C ($CDCl_3$): 14.04, 15.05 (CH_3), 23.75, 29.89, 35.17 (CH_2), 123.64, 128.48, 128.54, 129.37, 130.65, 135.05, 136.22, 136.51, 137.48, 160.16, 164.00, 170.35 (C arom) ppm; *m/z* (EI, 70 eV): 370 ($M^{+\cdot}$, 6), 369 ($M^{+\cdot}-1$, 12), 355 ($M^{+\cdot}-CH_3^{\cdot}$, 9), 341 ($M^{+\cdot}-C_2H_5^{\cdot}$, 13), 327 ($M^{+\cdot}-C_3H_7^{\cdot}$, 100); Anal. calcd for $C_{21}H_{20}Cl_2N_2$, C 67.93% H 5.43% Cl 19.10% N 7.54%. Found C 66.93% H 5.12% Cl 18.70% N 7.23%.

3.1.16. 5-Methyl-4-pentyl-2,6-diphenyl-pyrimidine 4p. Reaction time: 36 h. Purification of crude product by recrystallization affords 1.1 g (87%) of title compound as yellow solid, mp 76–77°C (MeOH); ν (KBr): 2958, 1585, 1541, 1392, 1014, 763, 696 cm^1; δ_H ($CDCl_3$): 0.91 (m, 3H, CH_3), 1.45 (m, 4H, $2CH_2$), 1.88 (m, 2H, CH_2), 2.35 (s, 3H, CH_3), 2.90 (m, 2H, CH_2), 7.50 (m, 6H, arom), 7.73 (m, 2H, arom), 8.55 (m, 2H, arom) ppm; δ_C ($CDCl_3$): 14.08, 15.07 (CH_3), 22.62, 27.52, 31.86, 35.45 (CH_2), 123.43, 128.03, 128.17, 128.33, 128.74, 129.27, 129.93, 136.89, 138.28, 139.31, 165.12, 169.99 (C arom) ppm; *m/z* (EI, 70 eV): 316 ($M^{+\cdot}$, 12), 315 ($M^{+\cdot}-1$, 20), 301 ($M^{+\cdot}-CH_3^{\cdot}$, 5), 287 ($M^{+\cdot}-C_2H_5^{\cdot}$, 25), 273 ($M^{+\cdot}-C_3H_7^{\cdot}$, 31), 259 ($M^{+\cdot}-C_4H_9^{\cdot}$, 100), 77 ($C_6H_5^+$, 4); Anal. calcd for $C_{22}H_{24}N_2$, C 83.50% H 7.64% N 8.85%. Found C 84.57% H 7.21% N 8.23%.

3.1.17. 5-Methyl-4-pentyl-2,6-di-*p*-tolyl-pyrimidine 4q. Reaction time: 12 h. Purification of crude product by recrystallization affords 1.3 g (96%) of title compound as yellow solid, mp 76–77°C (MeOH); ν (KBr): 2931, 1541, 1396, 1186, 837, 790 cm^1; δ_H ($CDCl_3$): 0.93 (m, 3H, CH_3), 1.43 (m, 4H, $2CH_2$), 1.84 (m, 2H, CH_2), 2.34 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 2.88 (m, 2H, CH_2), 7.30 (m, 4H, arom), 7.73, 8.55 ($AA'XX'$, 4H) ppm; δ_C ($CDCl_3$): 14.09, 15.10, 21.36, 21.46 (CH_3), 22.63, 27.56, 31.88, 35.45 (CH_2), 122.98, 127.97, 128.84, 129.04, 129.24, 135.61, 136.53, 138.69, 139.93, 161.09, 165.12, 169.73 (C arom) ppm; *m/z* (EI, 70 eV): 344 ($M^{+\cdot}$, 16), 343 ($M^{+\cdot}-1$, 22), 329 ($M^{+\cdot}-CH_3^{\cdot}$, 6), 315 ($M^{+\cdot}-C_2H_5^{\cdot}$, 24), 301 ($M^{+\cdot}-C_3H_7^{\cdot}$, 32), 287 ($M^{+\cdot}-C_4H_9^{\cdot}$, 100), 118 (5), 91 ($C_7H_7^+$, 3); Anal. calcd for $C_{24}H_{28}N_2$, C 83.68% H 8.19% N 8.13%. Found C 84.25% H 8.97% N 7.23%.

3.1.18. 2,4-Bis-(4-chloro-phenyl)-5-methyl-6-pentyl-pyrimidine 4r. Reaction time: 36 h. Purification of crude product by recrystallization affords 1.4 g (93%) of title compound as white solid, mp 67–68°C (MeOH); ν (KBr): 2958, 1585, 1541, 1392, 1014, 763, 696 cm^1; δ_H ($CDCl_3$): 0.96 (m, 3H, CH_3), 1.45 (m, 4H, $2CH_2$), 1.88 (m, 2H, CH_2), 2.35 (s, 3H, CH_3), 2.90 (m, 2H, CH_2), 7.50 (m, 6H, arom), 7.73 (m, 2H, arom), 8.55 (m, 2H, arom) ppm; δ_C ($CDCl_3$): 14.07, 15.07 (CH_3), 22.60, 27.45, 31.82, 35.43 (CH_2), 123.46, 128.48, 128.54, 129.36, 129.69, 130.66, 133.38, 136.21, 136.55, 160.58, 163.97, 170.38 (C arom) ppm; *m/z* (EI, 70 eV): 384 ($M^{+\cdot}$, 7), 383 ($M^{+\cdot}-1$, 11), 369 ($M^{+\cdot}-CH_3^{\cdot}$, 4), 355 ($M^{+\cdot}-C_2H_5^{\cdot}$, 18), 341 ($M^{+\cdot}-C_3H_7^{\cdot}$, 24), 327 ($M^{+\cdot}-C_4H_9^{\cdot}$, 100); Anal. calcd for $C_{22}H_{22}Cl_2N_2$, C 68.57% H 5.75% Cl 18.40% N 7.27%. Found C 67.86% H 5.21% Cl 19.32% N 7.86%.

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