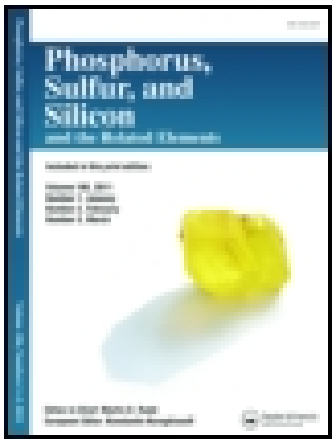

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MICHAEL ADDITION OF ACTIVATED NITRILES TO 4[(+)-CAMPHOR-10′-SULFONYLAMINO]-ACETOPHENONE AND SOME OF ITS CHALCONES

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*4-[(+)-Camphor-10′-sulfonylamino]acetophenone (**2**) and some of its chalcones **3** were easily prepared in quantitative yields starting from (+)-camphor-10-sulfonyl chloride. Several new 2-oxo-, 2-thio-, as well as 2-amino-pyridines carrying the camphor sulfonylamino group as a substituent were synthesized easily in one step by Michael addition of several activated nitriles to compounds **2** and **3**. The synthesis of some fused pyridines also was investigated.*

Keywords: α,β-unsaturated ketones; activated nitriles; camphor-10-sulfonyl chloride; deazapyrimidines; pyridinethiones; pyridones

Over the last decade there has been widespread interest to the synthesis of substituted-3-deazapyrimidines because of their potent biological effects.[1–7] Although many homochiral camphor-based derivatives have been used extensively in asymmetric synthesis as either chiral auxiliaries or ligands in enantioselective catalysis,[8–13] the use of camphor as a substituent in heterocyclic compounds has been poorly studied. As a part of our research directed at the development of new simple and efficient procedures for the synthesis of several deaza analogs and other antimetabolites,[14–18] we report herein on a convenient one-step synthesis of different new 2-oxo- and 2-thio-pyridines as well as the 2-aminopyridines, via Michael addition of activated nitriles to 4[(+)-camphor-10′-sulfonylamino]acetophenone and its chalcones by different synthetic routes. The present study also aimed to define the scope

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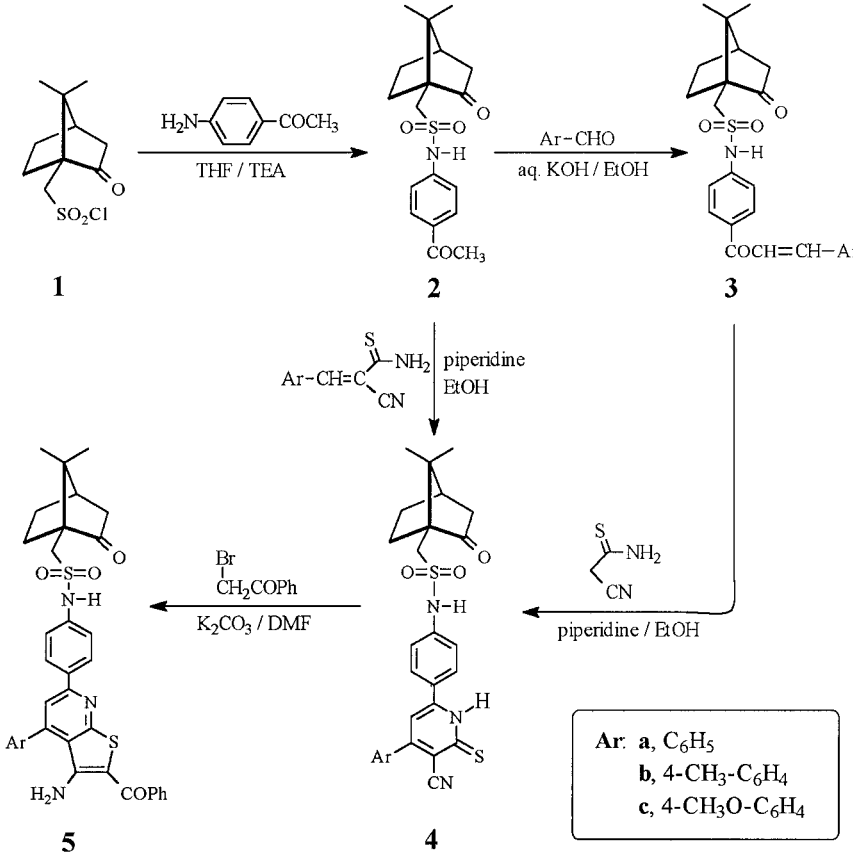
and limitation of our procedures for the synthesis of some fused pyridine derivatives.

RESULTS AND DISCUSSION

(+)-Camphor-10-sulfonyl chloride (**1**) was prepared according to the reported method[19]. Amidation of **1** with 4-aminoacetophenone smoothly afforded the corresponding 4-[(+)-camphor-10′-sulfonylamino]acetophenone (**2**) as the sole product. The IR spectrum of the sulfonamide **2** revealed the presence of strong absorptions at 1675 and 1740 cm^{-1} assignable for the acetyl and camphor carbonyls, respectively. ^{13}C-NMR spectrum also shows the characteristic signals at 196.93 and 206.02 ppm attributed to the carbonyl groups of acetyl and camphor moiety, respectively, indicating that the carbonyl of camphor moiety was not involved in such reaction. Chalcones **3a–c** have been prepared by the Claisen-Schmidt condensation of **2** with arylaldehydes in refluxing ethanol (Scheme 1). The structure of chalcones **3a–c** was supported by microanalytical and spectral data (see Experimental).

As a part of this program directed to the synthesis of some pyridin-2(1*H*)thiones, the synthesized acetophenone derivative **2** and its chalcones **3a–c** were subjected to reactions with cyanothioacetamide and some of its arylidenes. Thus, it has been found that compound **2** reacts with 3-arylidenecyanothioacetamide in boiling ethanol containing catalytic amounts of piperidine to yield a product for which the pyridin-2(1*H*)thione structure **4** was considered (Scheme 1). Structure **4c**, for example, was established based on ^{1}H-NMR which revealed the characteristic singlet signals at 6.95 and 12.24 ppm assigned to the pyridine 5-H and NH protons, respectively. Moreover, ^{13}C-NMR spectrum of **4c** shows the characteristic signals at 118.15 and 182.59 ppm attributed for the CN and C=S groups, respectively, of pyridine moiety. Formation of the pyridin-2(1*H*)thiones **4a–c** from the above reaction is assumed to proceed via Michael adduct[20–22] by initial addition of the methyl function in **2** to the activated double bond in the arylidenecyanothioacetamide followed by spontaneous cyclization, dehydration, and dehydrogenation to furnish the final isolable pyridin-2(1*H*)thione derivatives **4a–c**. The reaction is very simple to perform and the pyridin-2(1*H*)thiones **4a–c** precipitated in good yields from the reaction mixture. It is worth mentioning that the synthesis of compounds **4a–c** also could be achieved by reacting the chalcones **3a–c** with cyanothioacetamide in refluxing ethanol containing catalytic amounts of piperidine (Scheme 1). Microanalytical and spectral data also



SCHEME 1

were found to be in agreement with the pyridin-2(1*H*)thione structures **4a–c**.

Compound **4**, with its latent functional substituent, was found to be useful for the synthesis of fused pyridines. Thus, when compounds **4a–c** were subjected to the action of phenacyl bromide as alkylating agent, the *S*-alkylated derivatives were not isolated, but cyclization to the corresponding thieno[2,3-b]pyridine derivatives **5a–c** occurred (Scheme 1). The IR spectrum of the thienopyridine **5c**, for example, revealed the absence of a cyano band while ^{1}H-NMR revealed the complete absence of the pyridine NH signal in addition to the appearance of new broad singlet signal at 6.54 ppm assignable to the amino function.

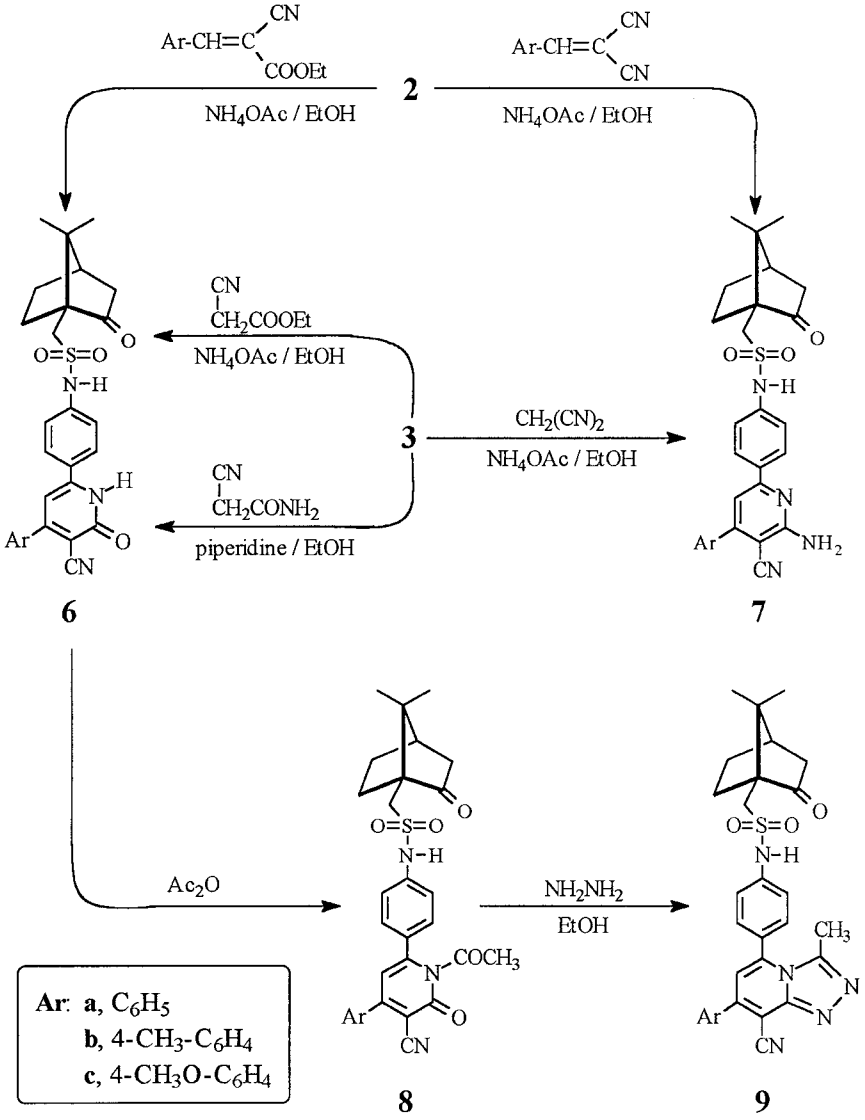
In another approach to the synthesis of some new substituted 2-oxo- and 2-amino-pyridines, compounds **2** and **3** were subjected

to the reaction with ethylcyanoacetate and some of its arylidenes, cyanoacetamide, as well as malononitrile. Under appropriate reaction conditions, the study of such reaction also has been reported to involve Michael addition followed by spontaneous cyclization, dehydration, and dehydrogenation.[21,23,24] Thus, the above-mentioned reaction was investigated. In a one-step synthesis, reaction of **2** with 3-arylideneethylcyanoacetates in presence of excess ammonium acetate afforded the desired product which proved by microanalytical and spectral data to be the desirable 4,6-disubstituted-3-cyano-2(1*H*)pyridones (**6**) (Scheme 2).

^{1}H-NMR spectrum of 3-cyanopyridone **6a** revealed the characteristic signals at 6.66 and 12.13 ppm assigned to the pyridone 5-H and N-H protons, respectively. Moreover, ^{13}C-NMR spectrum showed the signals at 117.52 and 166.37 ppm attributed to the cyano and carbonyl groups, respectively, of the pyridone moiety. It is noteworthy that, under similar reaction conditions, cyclocondensation of chalcones **3a–c** with ethylcyanoacetate yielded the same 3-cyano-2-pyridones **6a–c** in good yields (Scheme 2). The preparation of the same pyridones **6a–c** also was further achieved in a single step by reacting chalcones **3a–c** with cyanoacetamide in boiling ethanol containing catalytic amounts of piperidine (Scheme 2). In all cases, microanalytical and spectral data of the isolated products were found to be identical and in agreement with the pyridone structure **6**.

Reaction of compound **2** with arylidenemalononitriles in absolute ethanol and in the presence of excess amount of ammonium acetate also was investigated and smoothly led to the formation of the corresponding 2-aminopyridines **7a–c** in high yields (Scheme 2). ^{1}H-NMR spectrum of **7b** showed, in addition to a signal assignable to the pyridine 5-H, a broad singlet signal at 6.49 ppm attributed to an amino group and its ^{13}C-NMR revealed the characteristic signal at 116.97 ppm assigned to the cyano group. Under similar reaction conditions, 2-aminopyridines **7a–c** also could be obtained by the reaction of chalcones **3a–c** with malononitrile in presence of excess amount of ammonium acetate (Scheme 2).

Finally, the preparation of well crystalline 1,2,4-triazolo[4,3-a]pyridines **9a–c** were achieved by acetylation of compounds **6a–c** using acetic anhydride followed by treatment of the obtained *N*-acetyl derivatives **8a–c** with hydrazine hydrate (Scheme 2). The IR spectra of the 1,2,4-triazolo[4,3-a]pyridines **9a–c** revealed, in addition to the complete absence of the acetyl and pyridone carbonyl bands of compounds **8a–c**, a characteristic band at 2220 cm^{-1} attributed for the cyano group. The structural assignment of the final products **9a–c** also was based on ^{1}H-NMR spectral data (see Experimental).



SCHEME 2

In conclusion, the synthesized compounds obtained through these results contain (+)-camphor-10-sulfonylamino group as a substituent have high potential synthetic value and seem promising for further chemical transformation as well as for biological evaluation studies. Further works in this area are in progress.

EXPERIMENTAL

Melting points are uncorrected. TLC (thin layer chromatography) was carried out using Merck precoated silica gel plates (Merck 5554, $60F_{254}$) and the spots were detected with UV model UVGL-58. IR spectra were recorded on Perkin-Elmer 1430 spectrophotometer using the KBr Wafer Technique. ^{1}H- and ^{13}C-NMR spectra were recorded on a Varian EM-400 MHz spectrometer using TMS as an internal reference and chemical shifts are expressed in δ ppm units. Microanalytical data were obtained by the microanalytical center at Cairo University. Molecular rotation data were recorded at 20°C on a Perkin-Elmer 241 Polarimeter (concentrations are given as g/100 ml of solvent).

Synthesis of 4-[(+)-Camphor-10′-sulfonylamino]acetophenone (2)

To a solution of (+)-camphor-10-sulfonyl chloride (**1**) (10 mmol) in 50 ml of dry tetrahydrofuran cooled at 0°C was added triethylamine (1.4 ml, 10 mmol) and 4-aminoacetophenone (10 mmol). The reaction mixture was stirred for 3 h at room temperature and then quenched with 2N-HCl (25 ml). After evaporation of THF under vacuum, the resulting aqueous solution was extracted with ether (3 × 25 ml). The combined extracts were dried over $MgSO_4$ and evaporated under reduced pressure to leave the crude product **2** which was crystallized from $EtOH/H_2O$.

m.p. 118°C; yield (3.35 g, 96%); $[\alpha]_D$ − 64.5 (*c* 0.57, MeOH); (Found: C, 61.90; H, 6.58; N, 4.07; S, 9.17. Calc. for $C_{18}H_{23}NO_4S$: C, 61.87; H, 6.63; N, 4.01; S, 9.18%); ν_{max}/cm^{-1} 3165 (NH), 1740 (CO, camphor), 1675 (CO, acetyl); δ_H ($CDCl_3$) 0.94 (s, 3H, 8′-CH_3), 1.04 (s, 3H, 9′-CH_3), 1.4–1.6 (m, 1H, CH), 1.95–2.2 (m, 5H, CH + $2CH_2$), 2.4–2.5 (m, 1H, CH), 2.64 (s, 3H, $COCH_3$), 2.85 (d, 1H, *J* 16, CH), 3.2 (d, 1H, $J = 16$ Hz, CH), 7.31 (d, 2H, $J = 8.31$ Hz, Ar-H), 7.76 (d, 2H, $J = 8.31$ Hz, Ar-H), 7.85 (s, 1H, NH); δ_C 19.07 (C-9′), 19.73 (C-8′), 25.35 (CH_3CO), 27.56 (C-5′), 32.1 (C-6′), 35.74 (C-3′), 43.09 (C-4′), 47.33 (C-7′), 48.66 (C-10′), 58.87 (C-1′), 126.2, 127.97, 129.09, 137.35 ($C_{arom.}$), 196.93 (CH_3CO), 206.1 (C-2′).

Synthesis of the Chalcones 3 (General Procedure)

Few drops of 50% aqueous solution of potassium hydroxide were added to a mixture of **2** (10 mmol) and arylaldehyde (10 mmol) in 50 ml of ethanol. The reaction mixture was heated under reflux for 10 min. The resulting yellowish white solid that separated on cooling was filtered off and recrystallized from ethanol to afford the chalcone **3**.

3a: m.p. 158°C; yield (4.07 g, 93%); $[\alpha]_D$ − 95.8 (*c* 0.45, CH_2Cl_2); (Found: C, 68.67; H, 6.20; N, 3.24; S, 7.30. Calc. for $C_{25}H_{27}NO_4S$: C, 68.62; H, 6.22; N, 3.20; S, 7.33%); ν_{max}/cm^{-1} 3200 (NH), 1735 (CO, camphor), 1640 (Ar-CO); δ_H ($CDCl_3$) 0.89 (s, 3H, 8′-CH_3), 0.93 (s, 3H, 9′-CH_3), 1.4–1.55 (m, 1H, CH), 1.94–2.26 (m, 4H, $2CH_2$), 2.48–2.61 (m, 2H, CH_2), 2.81 (br, s, 1H, NH), 2.95 (d, 1H, $J = 14$ Hz, CH), 3.22 (d, 1H, $J = 14$ Hz, CH), 6.59 (d, 1H, $J = 10.7$ Hz, CH=C), 7.02 (d, 1H, $J = 10.9$ Hz, CH=C), 7.04–7.87 (m, 9H, $H_{arom.}$); δ_C 18.71 (C-9′), 19.15 (C-8′), 27.69 (C-5′), 31.73 (C-6′), 36.34 (C-3′), 43.51 (C-4′), 46.75 (C-7′), 49.03 (C-10′), 58.68 (C-1′), 126.91, 128.16, 129.55, 130.82, 131.20, 133.05, 133.36 ($C_{arom.}$), 136.94 (Ar*C*H), 137.53 (ArCO*C*H), 198.19 (Ar*C*O), 205.37 (C-2′).

3b: m.p. 187°C; yield (4.29 g, 95%); $[\alpha]_D$ − 49.3 (*c* 1.05, CH_2Cl_2); (Found: C, 69.17; H, 6.38; N, 3.12; S, 7.05. Calc. for $C_{26}H_{29}NO_4S$: C, 69.15; H, 6.47; N, 3.10; S, 7.10%); ν_{max}/cm^{-1} 3180 (NH), 1730 (CO, camphor), 1640 (Ar-CO); δ_H ($CDCl_3$) 0.94 (s, 3H, 8′-CH_3), 1.03 (s, 3H, 9′-CH_3), 1.33–2.62 (m, 10H, CH + $3CH_2$ + Ar-CH_3), 2.86 (br, s, 1H, NH), 3.11 (d, 1H, $J = 14$ Hz, CH), 3.28 (d, 1H, $J = 14$ Hz, CH), 6.34 (d, 1H, J 10.7, CH=C), 6.91 (d, 1H, $J = 10.9$ Hz, CH=C), 7.09–7.78 (m, 8H, $H_{arom.}$); δ_C 18.09 (C-9′), 19.31 (C-8′), 21.74 (Ar-*C*H_3), 27.16 (C-5′), 31.23 (C-6′), 35.92 (C-3′), 44.19 (C-4′), 47.22 (C-7′), 48.54 (C-10′), 59.16 (C-1′), 125.03, 127.22, 129.05, 132.10, 132.23, 133.09 ($C_{arom.}$), 135.55 (Ar*C*H), 138.92 (ArCO*C*H), 196.03 (Ar*C*O), 205.91 (C-2′).

3c: m.p. 141°C; yield (4.44 g, 95%); $[\alpha]_D$ − 58.5 (*c* 0.59, CH_2Cl_2); (Found: C, 66.77; H, 6.28; N, 3.00; S, 6.90. Calc. for $C_{26}H_{29}NO_5S$: C, 66.79; H, 6.25; N, 2.99; S, 6.86%); ν_{max}/cm^{-1} 3220 (NH), 1730 (CO, camphor), 1645 (Ar-CO); δ_H ($CDCl_3$) 0.88 (s, 3H, 8′-CH_3), 0.95 (s, 3H, 9′-CH_3), 1.35–1.85 (m, 5H, CH + $2CH_2$), 2.11–2.43 (m, 2H, CH_2), 2.60 (br, s, 1H, NH), 3.31 (d, 1H, $J = 14$ Hz, CH), 3.52 (d, 1H, $J = 14$ Hz, CH), 3.75 (s, 3H, OCH_3), 6.12 (d, 1H, $J = 10.7$ Hz, CH=C), 6.77 (d, 1H, $J = 10.9$ Hz, CH=C), 7.14–8.01 (m, 8H, $H_{arom.}$), δ_C 18.85 (C-9′), 19.71 (C-8′), 27.24 (C-5′), 32.54 (C-6′), 35.61 (C-3′), 42.08 (C-4′), 47.64 (C-7′), 49.62 (C-10′), 55.59 (O*C*H_3), 59.89 (C-1′), 124.04, 125.09, 127.32, 128.17, 128.59, 131.15, 133.65, 135.49 ($C_{arom.}$), 136.63 (Ar*C*H), 137.07 (ArCO*C*H), 193.78 (Ar*C*O), 204.11 (C-2′).

Synthesis of 4,6-Disubstituted-3-cyanopyridin-2(1*H*)thiones (4) (General Procedure)

To a mixture of **2** (10 mmol) and 3-arylidenecyanothioacetamide (10 mmol) in absolute ethanol (50 ml), a few drops of piperidine were added. The reaction mixture was heated under reflux for 4 h. The precipitated solid that separated on cooling was filtered off and recrystallized

from ethanol to afford the products **4a** (4.81 g, 93%), **4b** (4.89 g, 92%), and **4c** (4.93 g, 90%), respectively.

The same procedure described above was applied as well to the reaction of cyanothioacetamide (10 mmol) with the appropriate chalcone **3** (10 mmol). After refluxing for 5 h and the usual work-up procedure, the same products **4a** (4.55 g, 88%), **4b** (4.84 g, 91%), and **4c** (5.04 g, 92%), respectively, were obtained.

4a: m.p. 192°C; $[\alpha]_D$ − 99.3 (*c* 0.85, $CHCl_3$); (Found: C, 64.99; H, 5.26; N, 8.13; S, 12.40. Calc. for $C_{28}H_{27}N_3O_3S_2$: C, 64.96; H, 5.26; N, 8.12; S, 12.39%); ν_{max}/cm^{-1} 3280 (NH), 2220 (CN), 1720 (CO).

4b: m.p. 139°C; $[\alpha]_D$ − 103.9 (*c* 0.69, $CHCl_3$); (Found: C, 65.57; H, 5.47; N, 7.93; S, 12.10. Calc. for $C_{29}H_{29}N_3O_3S_2$: C, 65.51; H, 5.50; N, 7.90; S, 12.06%); ν_{max}/cm^{-1} 3260 (NH), 2225 (CN), 1720 (CO); δ_H ($CDCl_3$) 0.79 (s, 3H, 8′-CH_3), 0.91 (s, 3H, 9′-CH_3), 1.13–1.25 (m, 1H, CH), 1.34–1.95 (m, 5H, CH + $2CH_2$), 2.14–2.61 (m, 5H, CH + SO_2NH + $ArCH_3$), 3.08 (d, 1H, J = 13.5 Hz, CH), 3.17 (d, 1H, J = 13.5 Hz, CH), 6.82 (s, 1H, pyridine 5-H), 7.22–8.18 (m, 8H, $H_{arom.}$), 13.25 (s, br, 1H, NH); δ_C 18.64 (C-9′), 19.53 (C-8′), 21.99 (Ar*C*H_3), 27.66 (C-5′), 31.81 (C-6′), 36.9 (C-3′), 44.48 (C-4′), 46.32 (C-7′), 48.71 (C-10′), 59.90 (C-1′), 105.81 (C-3), 116.39 (CN), 120.45, 122.74, 125.47, 127.62, 130.29, 134.76 ($C_{arom.}$), 141.32 (C-5), 145.91 (C-4), 154.85 (C-6), 180.39 (C-2), 209.54 (C-2′).

4c: m.p. 167°C; $[\alpha]_D$ − 39.7 (*c* 0.95, $CHCl_3$); (Found: C, 63.61; H, 5.28; N, 7.63; S, 11.70. Calc. for $C_{29}H_{29}N_3O_4S_2$: C, 63.60; H, 5.34; N, 7.67; S, 11.71%); ν_{max}/cm^{-1} 3250 (NH), 2220 (CN), 1725 (CO); δ_H ($CDCl_3$) 0.85 (s, 3H, 8′-CH_3), 0.97 (s, 3H, 9′-CH_3), 1.38–2.48 (m, 7H, CH + $3CH_2$), 2.85 (br, s, 1H, SO_2NH), 3.38 (d, 1H, J = 13.5 Hz, CH), 3.56 (d, 1H, J = 13.5 Hz, CH), 3.85 (s, 3H, OCH_3), 6.95 (s, 1H, pyridine 5-H), 7.15–8.11 (m, 8H, $H_{arom.}$), 12.24 (br, s, 1H, NH); δ_C 18.75 (C-9′), 19.83 (C-8′), 27.42 (C-5′), 31.98 (C-6′), 35.90 (C-3′), 45.88 (C-4′), 46.74 (C-7′), 49.04 (C-10′), 56.34 (O*C*H_3), 59.83 (C-1′), 104.57 (C-3), 118.15 (CN), 126.05, 127.80, 128.83, 129.14, 131.62, 133.16, 134.56 ($C_{arom.}$), 142.82 (C-5), 147.11 (C-4), 154.37 (C-6), 182.59 (C-2), 211.35 (C-2′).

Synthesis of 2,4-Disubstituted-5-amino-6-benzoylthieno[2,3-b]pyridines (5) (General Procedure)

A mixture of pyridin-2(1*H*)thione **4** (10 mmol), K_2CO_3 (0.02 mmol), and phenacyl bromide (0.01 mmol) in dry DMF (50 ml) was stirred overnight at room temperature and then diluted with ice-cold water (50 ml). The resulting solid product was collected by filtration and crystallized from methanol to afford **5**.

5a: m.p. 178°C; yield (5.79 g, 91%); $[\alpha]_D - 28.1$ (*c* 0.35, $CHCl_3$); (Found: C, 68.05; H, 5.22; N, 6.65; S, 10.12. Calc. for $C_{36}H_{33}N_3O_4S_2$: C, 68.01; H, 5.23; N, 6.61; S, 10.09%); ν_{max}/cm^{-1} 3320 (NH_2), 3150 (NH), 1725 (CO, camphor), 1670 (CO, benzoyl); δ_H ($CDCl_3$) 0.86 (s, 3H, 8′-CH_3), 0.92 (s, 3H, 9′-CH_3), 1.03–1.56 (m, 2H, CH_2), 1.73–1.99 (m, 3H, CH + CH_2), 2.12–2.57 (m, 3H, CH_2 + SO_2NH), 3.16 (d, 1H, $J = 14$ Hz, CH), 3.37 (d, 1H, $J = 14$ Hz, CH), 6.77 (br, s, 2H, NH_2), 7.01 (s, 1H, pyridine 5-H), 7.19–8.13 (m, 14H, $H_{arom.}$).

5b: m.p. 147°C; yield (5.85 g, 90%); $[\alpha]_D - 74.3$ (*c* 0.66, $CHCl_3$); (Found: C, 68.35; H, 5.37; N, 6.45; S, 9.80. Calc. for $C_{37}H_{35}N_3O_4S_2$: C, 68.39; H, 5.43; N, 6.45; S, 9.87%); ν_{max}/cm^{-1} 3350 (NH_2), 3150 (NH), 1730 (CO, camphor), 1660 (CO, benzoyl).

5c: m.p. 132°C; yield (6.26 g, 94%); $[\alpha]_D - 33.4$ (*c* 0.57, $CHCl_3$); (Found: C, 66.80; H, 5.32; N, 6.28; S, 9.60. Calc. for $C_{37}H_{35}N_3O_5S_2$: C, 66.74; H, 5.30; N, 6.31; S, 9.63%); ν_{max}/cm^{-1} 3330 (NH_2), 3130 (NH), 1730 (CO, camphor), 1660 (CO, benzoyl); δ_H ($CDCl_3$) 0.97 (s, 3H, 8′-CH_3), 1.02 (s, 3H, 9′-CH_3), 1.16–1.68 (m, 3H, CH + CH_2), 2.07–2.66 (m, 5H, SO_2NH + $2CH_2$), 3.41 (d, 1H, $J = 14$ Hz, CH), 3.53 (d, 1H, $J = 14$ Hz, CH), 4.03 (s, 3H, OCH_3), 6.54 (br, s, 2H, NH_2), 6.88 (s, 1H, pyridine 5-H), 7.06–8.21 (m, 13H, $H_{arom.}$).

Synthesis of 4,6-Disubstituted-3-cyano-2(1*H*)pyridones (6)

Method A (General Procedure)

To a mixture of **2** (10 mmol) and ammonium acetate (30 mmol) in 50 ml of absolute ethanol was added 3-arylideneethylcyanoacetate (10 mmol). The reaction mixture was heated under reflux for 4 h and then left to cool. The separated solid was filtered off and dried. After recrystallization from ethanol, the pyridones **6a** (4.51 g, 90%), **6b** (4.85 g, 94%), and **6c** (4.94 g, 93%), respectively, were obtained.

The same procedure described above was applied as well to the reaction of ethylcyanoacetate (10 mmol) with the appropriate chalcone **3** (10 mmol). After refluxing for 6 h and the usual work-up procedure, the same products **6a** (4.46 g, 89%), **6b** (4.69 g, 91%), and **6c** (4.89 g, 92%), respectively, were obtained.

Method B (General Procedure)

To the appropriate chalcone **3** (5 mmol) in 25 ml of absolute ethanol, 5 mmol of cyanoacetamide and a few drops of piperidine were added. The reaction mixture was heated to reflux for 12 h. The pyridone **6** precipitated on cooling was collected by filtration. A further crop of product could be obtained by evaporation of the mother liquors. The combined

crops were crystallized from ethanol to afford the same products **6a** (4.46 g, 89%), **6b** (4.85 g, 94%), and **6c** (4.78 g, 90%), respectively.

6a: m.p. 191°C; $[\alpha]_D$ − 94.7 (*c* 1.03, CH_2Cl_2); (Found: C, 67.07; H, 5.41; N, 8.40; S, 6.35. Calc. for $C_{28}H_{27}N_3O_4S$: C, 67.05; H, 5.42; N, 8.38; S, 6.39%); ν_{max}/cm^{-1} 3200 (NH), 2215 (CN), 1725 (CO, camphor), 1650 (CO, pyridone); δ_H (DMSO) 0.90 (s, 3H, 8′-CH_3), 0.95 (s, 3H, 9′-CH_3), 1.03–1.55 (m, 3H, CH + CH_2), 1.73–2.5 (m, 4H, 2CH_2), 3.29 (d, 1H, $J = 14$ Hz, CH), 3.44 (d, 1H, $J = 14$ Hz, CH), 4.89 (br, s, 1H, SO_2NH), 6.66 (s, 1H, pyridone 5-H), 7.17–8.02 (m, 9H, $H_{arom.}$), 12.13 (br, s, 1H, pyridone NH); δ_C 18.63 (C-9′), 19.40 (C-8′), 26.81 (C-5′), 30.94 (C-6′), 34.55 (C-3′), 41.97 (C-4′), 46.70 (C-7′), 48.14 (C-10′), 58.20 (C-1′), 107.08 (C-3), 113.34 (C-4), 117.52 (CN), 127.95, 129.33, 130.52, 131.61, 133.21, 134.54, 137.86 ($C_{arom.}$), 147.16 (C-5), 151.46 (C-6), 166.37 (C-2), 211.40 (C-2′).

6b: m.p. 165°C; $[\alpha]_D$ − 87.2 (*c* .83, CH_2Cl_2); (Found: C, 67.58; H, 5.60; N, 8.20; S, 6.20. Calc. for $C_{29}H_{29}N_3O_4S$: C, 67.55; H, 5.67; N, 8.15; S, 6.22%); ν_{max}/cm^{-1} 3150 (NH), 2220 (CN), 1725 (CO, camphor), 1645 (CO, pyridone); δ_H (DMSO) 0.92 (s, 3H, 8′-CH_3), 0.97 (s, 3H, 9′-CH_3), 1.02–1.56 (m, 3H, CH + CH_2), 1.70–2.65 (m, 7H, 2CH_2 + ArCH_3), 3.22 (d, 1H, $J = 14$ Hz, CH), 3.43 (d, 1H, $J = 14$ Hz, CH), 5.26 (br, s, 1H, SO_2NH), 6.42 (s, 1H, pyridone 5-H), 7.05–7.99 (m, 8H, $H_{arom.}$), 12.56 (br, s, 1H, pyridone NH); δ_C 18.70 (C-9′), 19.33 (C-8′), 22.65 (Ar-*C*H_3), 26.57 (C-5′), 31.61 (C-6′), 34.13 (C-3′), 42.50 (C-4′), 46.63 (C-7′), 47.41 (C-10′), 57.84 (C-1′), 105.57 (C-3), 114.72 (C-4), 118.01 (CN), 125.92, 127.13, 128.15, 130.01, 131.03, 132.99, 133.81 ($C_{arom.}$), 147.64 (C-5), 152.66 (C-6), 167.89 (C-2), 212.62 (C-2′).

6c: m.p. 142°C; $[\alpha]_D$ − 102.8 (*c* 1.66, CH_2Cl_2); (Found: C, 65.54; H, 5.49; N, 7.88; S, 6.10. Calc. for $C_{29}H_{29}N_3O_5S$: C, 65.52; H, 5.50; N, 7.90; S, 6.03%); ν_{max}/cm^{-1} 3200 (NH), 2220 (CN), 1720 (CO, camphor), 1650 (CO, pyridone); δ_H (DMSO) 0.95 (s, 3H, 8′-CH_3), 1.03 (s, 3H, 9′-CH_3), 1.22–2.49 (m, 7H, CH + 3CH_2), 3.03 (d, 1H, $J = 14$ Hz, CH), 3.28 (d, 1H, $J = 14$ Hz, CH), 3.72 (s, 3H, OCH_3), 5.02 (br, s, 1H, SO_2NH), 6.60 (s, 1H, pyridone 5-H), 6.98–7.89 (m, 8H, $H_{arom.}$), 12.85 (br, s, 1H, pyridone NH); δ_C 18.62 (C-9′), 19.13 (C-8′), 26.27 (C-5′), 30.63 (C-6′), 33.71 (C-3′), 42.80 (C-4′), 47.05 (C-7′), 48.96 (C-10′), 55.52 (O*C*H_3), 58.20 (C-1′), 108.33 (C-3), 113.58 (C-4), 117.62 (CN), 124.03, 127.04, 129.42, 130.08, 130.94, 131.50, 134.08 ($C_{arom.}$), 150.14 (C-5), 152.31 (C-6), 163.82 (C-2), 213.85 (C-2′).

Synthesis of 4,6-Disubstituted-2-amino-3-cyanopyridines (7) (General Procedure)

A mixture of **2** (10 mmol), arylidenemalononitirile (10 mmol), and ammonium acetate (20 mmol), absolute ethanol (50 ml) was heated under

reflux for 4 h. The reaction mixture was concentrated to one half of its volume. On cooling, the separated solid product was filtered off, dried, and recrystallized from ethanol to afford **7a** (4.61 g, 92%), **7b** (4.63 g, 90%), and **7c** (4.83 g, 91%), respectively.

The same procedure described above was applied as well to the reaction of malononitirile (10 mmol) with chalcone **3** (10 mmol). After refluxing for 6 h and the same work-up procedure, the same products **7a** (4.40 g, 88%), **7b** (4.68 g, 91%), and **7c** (4.93 g, 93%), respectively, were obtained.

7a: m.p. 231°C; $[\alpha]_D$–87.3 (*c* 1.5, $CHCl_3$); (Found: C, 67.20; H, 5.63; N, 11.16; S, 6.37. Calc. for $C_{28}H_{28}N_4O_3S$: C, 67.18; H, 5.64; N, 11.19; S, 6.40%); ν_{max}/cm^{-1} 3370 (NH_2), 3130 (NH), 2220 (CN), 1725 (CO).

7b: m.p. 175°C; $[\alpha]_D$ – 108.8 (*c* 1.75, $CHCl_3$); (Found: C, 67.74; H, 5.92; N, 10.86; S, 6.26. Calc. for $C_{29}H_{30}N_4O_3S$: C, 67.68; H, 5.87; N, 10.89; S, 6.23%); ν_{max}/cm^{-1} 3380 (NH_2), 3145 (NH), 2210 (CN), 1730 (CO); δ_H ($CDCl_3$) 0.87 (s, 3H, 8′-CH_3), 0.92 (s, 3H, 9′-CH_3), 1.21–2.42 (m, 7H, CH + 3CH_2), 2.49 (s, 3H, Ar-CH_3), 3.64 (d, 1H, J = 14 Hz, CH), 3.82 (d, 1H, J = 14 Hz, CH), 5.11 (br, s, 1H, NH), 6.49 (br, s, 2H, NH_2), 6.95–8.07 (m, 9H, $H_{arom.}$ + pyridine 5-H); δ_C 18.53 (C-9′), 19.34 (C-8′), 21.81 (Ar*C*H_3), 26.97 (C-5′), 31.19 (C-6′), 33.91 (C-3′), 43.11 (C-4′), 46.33 (C-7′), 48.56 (C-10′), 58.12 (C-1′), 116.97 (CN), 122.64 (C-4), 125.05, 128.86, 129.14, 131.76, 133.08, 134.56, 135.97 ($C_{arom.}$), 135.97 (C-5), 146.04 (C-3), 151.07 (C-6), 154.57 (C-2), 209.91 (C-2′).

7c: m.p. 202°C; $[\alpha]_D$ – 77.3 (*c* 1.34, CH_2Cl_2); (Found: C, 65.61; H, 5.69; N, 10.51; S, 6.00. Calc. for $C_{29}H_{30}N_4O_4S$: C, 65.64; H, 5.70; N, 10.56; S, 6.04%); ν_{max}/cm^{-1} 3350 (NH_2), 3140 (NH), 2220 (CN), 1725 (CO); δ_H ($CDCl_3$) 0.88 (s, 3H, 8′-CH_3), 0.94 (s, 3H, 9′-CH_3), 1.19–1.95 (m, 5H, CH + 2CH_2), 2.22–2.39 (m, 2H, CH_2), 3.59 (d, 1H, J = 14 Hz, CH), 3.77 (d, 1H, J = 14 Hz, CH), 3.99 (s, 3H, OCH_3), 5.27 (br, s, 1H, NH), 6.36 (br, s, 2H, NH_2), 7.00–8.09 (m, 9H, $H_{arom.}$ + pyridine 5-H); δ_C 17.56 (C-9′), 19.03 (C-8′), 27.45 (C-5′), 31.90 (C-6′), 34.22 (C-3′), 42.73 (C-4′), 46.57 (C-7′), 48.04 (C-10′), 56.85 (O*C*H_3), 59.06 (C-1′), 117.17 (CN), 122.29 (C-4), 125.55, 127.66, 129.02, 129.18, 132.10, 133.09, 134.12 ($C_{arom.}$), 132.30 (C-5), 142.87 (C-3), 150.45 (C-6), 155.15 (C-2), 210.15 (C-2′).

Synthesis of 4,6-Disubstituted-1-acetyl-3-cyanopyridin-2-ones (8) (General Procedure)

A mixture of pyridone **6** (10 mmol) and acetic anhydride (30 ml) was heated under reflux for 3 h. The reaction mixture was allowed to cool to room temperature and then poured onto ice-cold water. The separated solid was filtered off, dried, and crystallized from ethanol to afford **8**.

8a: m.p. 161°C; yield (5.16 g, 95%); $[\alpha]_D$ − 56 (*c* 1.25, CH_2Cl_2); (Found: C, 66.33; H, 5.37; N, 7.72; S, 5.84. Calc. for $C_{30}H_{29}N_3O_5S$: C, 66.28; H, 5.38; N, 7.73; S, 5.90%); ν_{max}/cm^{-1} 3170 (NH), 2215 (CN), 1735 (CO, camphor), 1695 (CO, acetyl), 1665 (CO, pyridone).

8b: m.p. 127°C; yield (5.35 g, 96%); $[\alpha]_D$ − 63 (*c* 1.51, CH_2Cl_2); (Found: C, 66.84; H, 5.58; N, 7.52; S, 5.77. Calc. for $C_{31}H_{31}N_3O_5S$: C, 66.78; H, 5.60; N, 7.53; S, 5.75%); ν_{max}/cm^{-1} 3150 (NH), 2220 (CN), 1745 (CO, camphor), 1700 (CO, acetyl), 1660 (CO, pyridone); δ_H ($CDCl_3$) 0.95 (s, 3H, 8′-CH_3), 1.05 (s, 3H, 9′-CH_3), 1.28–2.54 (m, 10H, CH + 3CH_2 + ArCH_3), 2.75 (s, 3H, CH_3CO), 3.55 (d, 1H, J = 13.5 Hz, CH), 3.71 (d, 1H, J = 13.5 Hz, CH), 5.33 (br, s, 1H, NH), 6.49 (br, s, 1H, pyridone 5-H), 6.99–8.13 (m, 8H, $H_{arom.}$); δ_C 17.89 (C-9′), 19.90 (C-8′), 22.42 (Ar*C*H_3), 26.90 (*C*H_3CO), 27.44 (C-5′), 32.80 (C-6′), 35.19 (C-3′), 42.07 (C-4′), 46.23 (C-7′), 48.07 (C-10′), 59.68 (C-1′), 104.69 (C-3), 111.54 (C-4), 115.87 (CN), 120.41, 122.08, 125.89, 127.86, 131.19, 132.45, 137.78 ($C_{arom.}$), 149.70 (C-5), 154.92 (C-6), 166.72 (C-2), 197.55 (*C*OMe), 210.97 (C-2′).

8c: m.p. 98°C; yield (5.45 g, 95%); $[\alpha]_D$ − 92.6 (*c* 1.34, CH_2Cl_2); (Found: C, 64.93; H, 5.48; N, 7.33; S, 5.60. Calc. for $C_{31}H_{31}N_3O_6S$: C, 64.90; H, 5.45; N, 7.32; S, 5.59%); ν_{max}/cm^{-1} 3150 (NH), 2210 (CN), 1740 (CO, camphor), 1690 (CO, acetyl), 1670 (CO, pyridone); δ_H ($CDCl_3$) 0.93 (s, 3H, 8′-CH_3), 0.99 (s, 3H, 9′-CH_3), 1.28–2.58 (m, 7H, CH + 3CH_2), 2.65 (s, 3H, CH_3CO), 3.32 (d, 1H, J = 13.5 Hz, CH), 3.49 (d, 1H, J = 13.5 Hz, CH), 3.95 (s, 3H, OCH_3), 5.15 (br, s, 1H, NH), 6.31 (br, s, 1H, pyridone 5-H), 7.05–8.04 (m, 8H, $H_{arom.}$); δ_C 18.40 (C-9′), 19.71 (C-8′), 27.30 (C-5′), 28.74 (*C*H_3CO), 32.69 (C-6′), 36.33 (C-3′), 42.59 (C-4′), 45.93 (C-7′), 47.90 (C-10′), 53.43 (O*C*H_3), 59.07 (C-1′), 106.75 (C-3), 114.52 (C-4), 116.87 (CN), 126.84, 127.57, 128.33, 128.55, 128.65, 130.17, 135.05 ($C_{arom.}$), 152.68 (C-5), 154.70 (C-6), 165.88 (C-2), 195.92 (*C*OMe), 210.08 (C-2′).

Synthesis of 5,7-Disubstituted-3-methyl-8-cyano-1,2,4-triazolo[4,3-a]pyridines (9) (General Procedure)

A mixture of **8** (10 mmol) and 98% hydrazine hydrate (3 ml) in absolute ethanol (30 ml) was heated under reflux for 6 h. The reaction mixture was left to cool and the separated solid product was filtered, dried, and recrystallized from methanol to afford **9**.

9a: m.p. 189°C; yield (4.75 g, 88%); $[\alpha]_D$ − 81.2 (*c* 0.92, CH_2Cl_2); (Found: C, 66.80; H, 5.42; N, 12.95; S, 5.91. Calc. for $C_{30}H_{29}N_5O_3S$: C, 66.77; H, 5.42; N, 12.98; S, 5.94%); ν_{max}/cm^{-1} 3130 (NH), 2220 (CN), 1725 (CO); δ_H (DMSO) 0.89 (s, 3H, 8′-CH_3), 0.95 (s, 3H, 9′-CH_3), 1.24–2.51 (m, 10H, CH + 3CH_2 + NCCH_3), 3.34 (d, 1H, J = 14 Hz, CH), 3.46

(d, 1H, $J = 14$ Hz, CH), 4.56 (br, s, 1H, NH), 6.89 (s, 1H, pyridine CH), 7.15–8.09 (m, 9H, $H_{arom.}$).

9b: m.p. 206°C; yield (4.82 g, 87%); $[\alpha]_D - 102.9$ (*c* 0.1.1, CH_2Cl_2); (Found: C, 67.29; H, 5.61; N, 12.64; S, 5.80. Calc. for $C_{31}H_{31}N_5O_3S$: C, 67.25; H, 5.64; N, 12.65; S, 5.79%); ν_{max}/cm^{-1} 3130 (NH), 2220 (CN), 1725 (CO).

9c: m.p. 155°C; yield (5.18 g, 91%); $[\alpha]_D - 55.8$ (*c* 1.22, CH_2Cl_2); (Found: C, 65.39; H, 5.51; N, 12.34; S, 5.60. Calc. for $C_{31}H_{31}N_5O_4S$: C, 65.36; H, 5.48; N, 12.29; S, 5.63%); ν_{max}/cm^{-1} 3130 (NH), 2220 (CN), 1730 (CO); δ_H (DMSO) 0.91 (s, 3H, 8′-CH_3), 0.97 (s, 3H, 9′-CH_3), 1.3–2.64 (m, 10H, CH + $3CH_2$ + $NCCH_3$), 3.38 (d, 1H, $J = 14$ Hz, CH), 3.59 (d, 1H, $J = 14$ Hz, CH), 4.03 (s, 3H, OCH_3), 5.15 (br, s, 1H, NH), 7.08–8.00 (m, 9H, $H_{arom.}$ + pyridine CH).

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