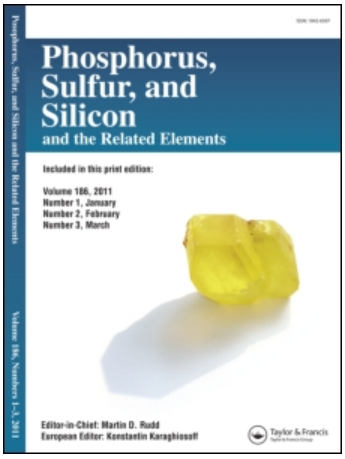

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A Novel One-Pot Synthesis of Polyfunctionally Substituted Thiopyrano(2,3- b)pyridine and Pyrido(2,3- b)pyridine Derivatives under Solid-Liquid Phase-Transfer Catalysis

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A NOVEL ONE-POT SYNTHESIS OF POLYFUNCTIONALLY SUBSTITUTED THIOPYRANO(2,3-b)PYRIDINE AND PYRIDO(2,3-b)PYRIDINE DERIVATIVES UNDER SOLID-LIQUID PHASE-TRANSFER CATALYSIS

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*Ketoketene thioacetals or cyanoketene thioacetals which were formed by treatment of a variety of active methylenes containing α-keto or α-cyano group with CS_2 or with PhNCS were allowed to react with 2-aminoprop-1-ene-1,1,3-tricarbonitrile under PTC conditions to afford thiopyrano(2,3-b)pyridine **3a–12a** or pyrido(2,3-b)pyridine **3b–12b** derivatives.*

Keywords: Kelēne thioacetals; phase-transfer catalysis (PTC); pyridopyridines; thiopyranopyridines

The synthesis of ketoketene[1] or cyanoketene S,S-acetals,[2] as well as heterocyclic ketene N,N-acetal[3–5] or N,S-acetals,[3,6,7] has attracted considerable attention since these acetals are used as versatile starting materials for the synthesis of a wide variety of fused heterocycles. Also, β-enaminonitriles have proven to be valuable synthons for the synthesis of a wide variety of unique heterocyclic systems, including pyrazoles,[8] imidazoles,[9] pyridines,[10] pyrimidines,[11] and thiophenes.[12–14] As an extension of our efforts directed towards the facile synthesis of heterocyclic ring systems under phase-transfer catalysis conditions (PTC),[15–22] we report herein the applicability of 2-aminoprop-1-ene-1,1,3-tricarbonitrile[23] as a synthon for the synthesis of various thiopyranopyridine or pyridopyridine and their fused derivatives.

Compounds **3a,b–12a,b** were prepared starting with ketothioacid (or amide) **1** or cyanothioacid (or amide) **2**, which were obtained via carbanions generated in situ, upon treatment of active methylenes containing α-keto or α-cyano groups with an equimolar amount of carbon

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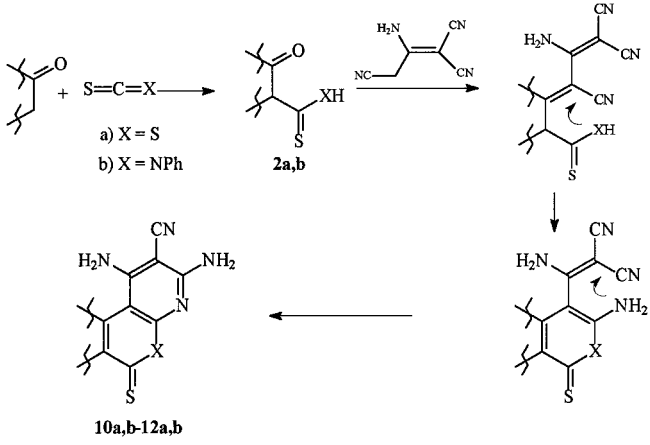
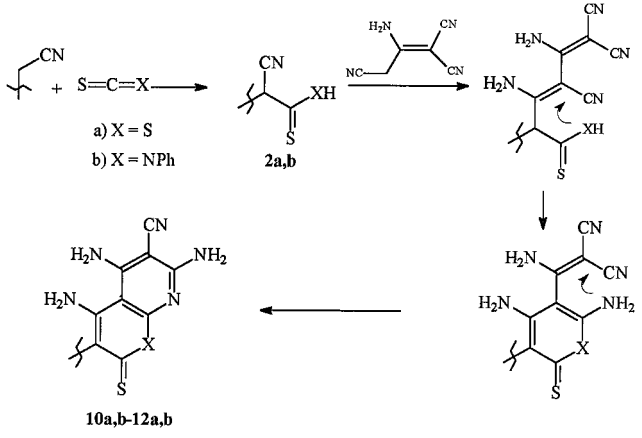
disulfide or phenyl isothiocyanate followed by adding equimolar ratio of 2-aminoprop-1-ene-1,1,3-tricarbonitrile in a one pot reaction using PTC conditions [K_2CO_3/dioxane/tetrabutylammonium bromide TBAB] in almost >80% yield (Schemes 3 and 4).

Notably, the active methylene in the enaminonitrile added to the carbonyl or to the cyano group in **1** or **2** rather than the addition of the amino group.[12,13,24] The fused thiopyranopyridine or pyridopyridine rings were formed most probably via nucleophilic attack of the -XH group on the cyano group of the enaminonitrile, followed by another nucleophilic attack of the formed $-NH_2$ group at the another cyano group of the intermediate (Schemes 1 and 2).

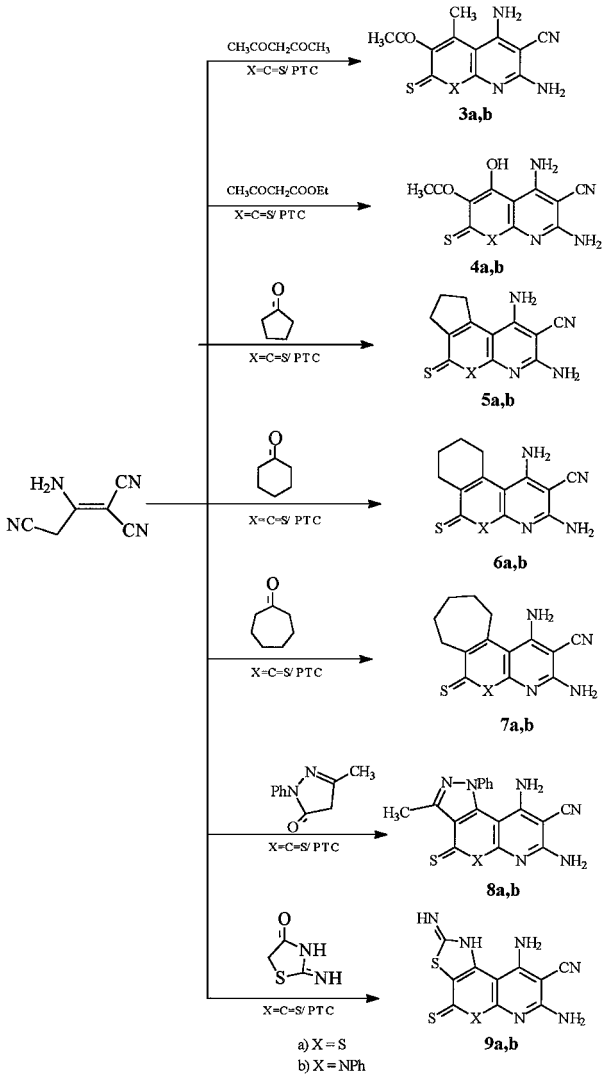


SCHEME 1



SCHEME 2

2-Aminoprop-1-ene-1,1,3-tricarbonitrile reacted with a variety of carbonyl containing active methylene compounds including acetylacetone, ethyl acetoacetate, cyclopentanone, cyclohexanone, cycloheptanone, 3-methyl-1-phenylpyrazol-5-one, and 2-iminothiazolidin-4-one using PTC conditions and afforded the desired thiopyrano (2,3-b)pyridine **3a–9a** or pyrido(2,3-b)pyridine **3b–9b** derivatives (Scheme 3).



SCHEME 3

EXPERIMENTAL

All melting points were determined on a Kofler melting point apparatus and were uncorrected. IR spectra were recorded on a Nicolet 710-FT IR spectrophotometer. ^{1}H NMR spectra were recorded on a Varian EM-360 A at 60 MHz spectrometer, using DMSO as solvent and TMS as internal standard. Elemental analyses were carried out with an elemental analyzer model 240 C.

Thiopyrano(2,3-b)pyridine and Pyrido(2,3-b)pyridine Derivatives 3a,b–12a,b

General Procedure

An equimolar mixture (0.05 mmol) of active methylene and CS_2 or PhNCS in 70 ml of dioxane was treated with 7 g of anhydrous K_2CO_3 and a catalytic amount of tetrabutylammonium bromide (TBAB, 3 mmol). The reaction mixture was stirred at different temperature for different periods of time (cf. Table I), and the formed dianionic ambident compound was then treated with (0.05 mmol) of 2-aminoprop-1-ene-1,1,3-tricarbonitrile. The reaction mixture was stirred at 60°C for 3 h and the dioxane layer was then separated by filtration and evaporated in vacuo. The K_2CO_3 layer was dissolved in water, the precipitate product was separated by filteration and the filtrate was acidified with dil. HCl.

All compounds were separated from the aqueous K_2CO_3 layer after dissolving in water and filtration except for compounds **4a**, **4b** which were separated from the acidified filtrate.

TABLE I Physical and Analytical Data of the Prepared Compounds

Comp no.	m.p (°C)[a]/ cryst. solvent[b]	Reaction time (h)	Reaction temp. (°C)	Comp no.	m.p (°C)[a]/ cryst. solvent[b]	Reaction time (h)	Reaction temp. (°C)
3a	312/A	1	25	**8a**	310/A	4	30
3b	333/A	1.5	25	**8b**	300/A	5	30
4a	272/B	3	28	**9a**	334/B	4	30
4b	287/B	3	30	**9b**	328/B	5	30
5a	306/A	2	25	**10a**	310/A	2	5–10
5b	319/A	3	30	**10b**	298/A	2	5–10
6a	290/C	2	25	**11a**	302/A	3	20
6b	321/C	3	30	**11b**	295/A	3	25
7a	315/C	2	25	**12a**	316/C	3	25
7b	311/C	3	30	**12b**	305/C	4	25

[a]Not corrected.
[b]A = Ethanol; B = Pyridine; C = Dioxane.

TABLE II Analytical and Spectral Data for the Newly Prepared Compounds

Product	Yield (%)	Mol. form.[a] mol. wt.	Analysis (%) calcd./found C	H	N	IR (KBr)[b]	^{1}H-NMR[c] DMSO-d_6
3a	94	$C_{12}H_{10}N_4OS_2$ 290.35	49.64 49.47	3.47 3.49	19.34 19.25	3446, 3350, 3230 ($2NH_2$), 2200 (CN), 1650 (C=O)	5.80-5.60 (br, 4H, $2NH_2$), 4.20-4.00 (br, 2H, NH_2), 2.80 (s, 3H, $COCH_3$), 2.10 (s, 3H, CH_3)
3b	89	$C_{18}H_{15}N_5OS$ 349.41	61.88 62.00	4.33 4.30	20.04 19.98	3410, 3320, 3250 ($2NH_2$), 2191 (CN), 1630 (C=O)	8.30-7.80 (m, 5H, arom.), 6.30-6.10 (br, 2H, NH_2), 4.80-4.60 (br, 2H, NH_2), 2.80 (s, 3H, $COCH_3$), 2.10 (s, 3H, CH_3)
4a	91	$C_{11}H_8N_4O_2S_2$ 292.34	45.19 44.99	2.76 2.79	19.16 19.20	3446 (OH), 3302, 3210, 3150 ($2NH_2$), 2196 (CN), 1650 (C=O)	6.40-6.20 (br, 4H, $2NH_2$), 4.50-4.30 (br, 2H, NH_2), 4.10 (s, 1H, OH), 2.80 (s, 3H, $COCH_3$), 2.10 (s, 3H, CH_3)
4b	85	$C_{17}H_{13}N_5O_2S$ 351.38	58.11 58.20	3.73 3.82	19.93 20.10	3450 (OH), 3420, 3310, 3240 ($2NH_2$), 2208 (CN), 1660 (C=O)	8.20-7.50 (m, 5H, arom.), 6.50-6.30 (br, 2H, NH_2), 4.50-4.20 (br, 2H, NH_2), 4.10 (s, 1H, OH), 3.40 (s, 3H, $COCH_3$), 2.10 (s, 3H, CH_3)
5a	81	$C_{12}H_{10}N_4S_2$ 274.35	52.50 52.52	3.69 3.65	20.41 20.22	3350, 3240, 3100 ($2NH_2$), 2950 (CH-aliph.), 2190 (CN)	6.20-6.00 (br, 2H, NH_2), 4.70-4.40 (br, 2H, NH_2), 3.20-2.80 (m, 4H, $2CH_2$), 0.80-0.60 (m, 2H, CH_2)
5b	83	$C_{18}H_{15}N_5S$ 333.42	64.84 64.72	4.53 4.62	21.00 20.84	3360, 3250, 3120 ($2NH_2$), 2960 (CH-aliph.), 2190 (CN)	8.00-7.30 (m, 5H, arom.), 6.40-6.20 (br, 2H, NH_2), 4.50-4.20 (br, 2H, NH_2), 3.20-2.90 (m, 4H, $2CH_2$), 0.90-0.70 (m, 2H, CH_2)

(Continued on next page)

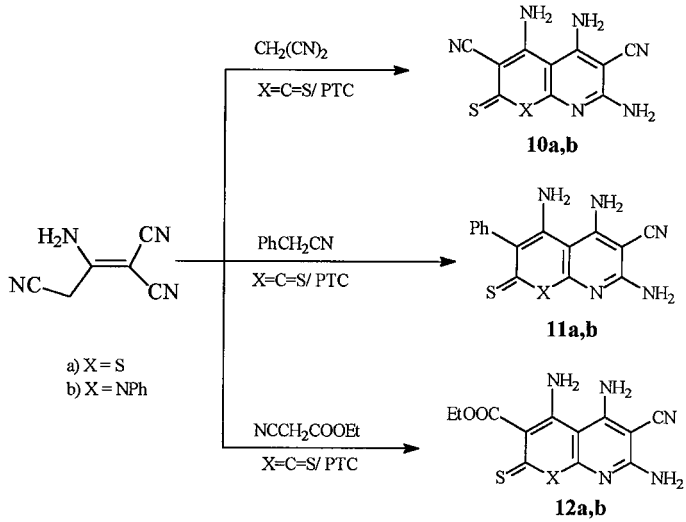
TABLE II Analytical and Spectral Data for the Newly Prepared Compounds *(Continued)*

Product	Yield (%)	Mol. form.[a] mol. wt.	Analysis (%) calcd./found C	H	N	IR (KBr)[b]	^{1}H-NMR[c] DMSO-d_6
6a	80	$C_{13}H_{12}N_4S_2$ 288.39	54.14 54.26	4.19 4.10	19.43 19.23	3360, 3250, 3100 ($2NH_2$), 2980 (CH-aliph.), 2220 (CN)	6.40-6.20 (br, 2H, NH_2), 4.60-4.40 (br, 2H, NH_2), 3.20-2.80 (m, 4H, $2CH_2$), 1.10-0.70 (m, 4H, $2CH_2$)
6b	88	$C_{19}H_{17}N_5S$ 347.43	65.69 65.58	4.93 5.12	20.16 20.19	3350, 3260, 3110 ($2NH_2$), 2960 (CH-aliph.), 2210 (CN)	8.10-7.50 (m, 5H, arom.), 6.40-6.20 (br, 2H, NH_2), 4.40-4.20 (br, 2H, NH_2), 3.30-2.90 (m, 4H, $2CH_2$), 1.00-0.60 (m, 4H, $2CH_2$)
7a	82	$C_{14}H_{14}N_4S_2$ 302.41 361.46	55.60 55.67 66.36	4.66 4.37 5.21	18.52 18.63 19.16	3340, 3250, 3100 ($2NH_2$), 2970 (CH-aliph.), 2222 (NH_2), 2980 (CH-aliph.), 2220 (CN)	6.30-6.00 (br, 2H, NH_2), 4.70-4.50 (br, 2H, NH_2), 7.80-7.30 (m, 5H, arom.), 6.20-6.00 (br, 2H, NH_2), 4.50-4.20 (br, 2H, NH_2), 3.30-2.80 (m, 4H, $2CH_2$), 1.10-0.70 (m, 6H, $3CH_2$)
8a	78	$C_{17}H_{12}N_6S_2$ 364.44	56.02 55.98	3.32 3.22	23.06 23.22	3320, 3225, 3180 ($2NH_2$), 3050 (CH-arom.), 2218 (CN)	8.00-7.50 (m, 5H, arom.), 6.20-6.00 (br, 2H, NH_2), 4.60-4.40 (br, 2H, NH_2), 1.90 (s, 3H, CH_3)
8b	80	$C_{23}H_{17}N_7S$ 423.49	65.23 65.33	4.04 3.98	23.15 23.33	3350, 3250, 3200 ($2NH_2$), 3070 (CH-arom.), 2210 (CN)	8.20-7.50 (m, 10H, arom.), 6.20-6.00 (br, 2H, NH_2), 4.50-4.20 (br, 2H, NH_2), 1.90 (s, 3H, CH_3)
9a	75	$C_{10}H_6N_7S_3$ 306.39	39.20 39.11	1.97 1.88	27.43 27.12	3350, 3250, 3200 ($2NH_2$), 3120, 3100 (2NH), 2220 (CN)	9.70 (br, 1H, NH), 9.20 (br, 1H, NH), 6.50-6.20 (br, 2H, NH_2), 4.60-4.40 (br, 2H, NH_2)

9b	73	$C_{16}H_{11}N_7S_2$ 365.43	52.58 52.44	3.03 3.12	26.83 27.00	3350, 3260, 3200 ($2NH_2$), 3120, 3100 (2NH), 2220 (CN), 1600 (C=N)	9.70 (br, 1H, NH), 9.30 (br, 1H, NH), 8.10-7.70 (m, 5H, arom.), 6.20-6.00 (br, 2H, NH_2), 4.30-4.00 (br, 2H, NH_2)
10a	77	$C_{10}H_6N_6S_2$ 274.31	43.78 43.45	2.20 2.31	30.63 30.43	3320, 3225, 3180 ($3NH_2$), 2220, 2210 (2CN)	6.40-6.00 (br, 4H, $2NH_2$), 4.60-4.40 (br, 2H, NH_2)
10b	79	$C_{16}H_{11}N_7S$ 333.37	57.64 57.66	3.32 3.12	29.41 29.34	3320, 3225, 3180 ($3NH_2$), 3050 (CH-arom.), 2220, 2200 (2CN)	7.80-7.30 (m, 5H, arom.), 6.20-5.90 (br, 4H, $2NH_2$), 4.40-4.20 (br, 2H, NH_2)
11a	86	$C_{15}H_{11}N_5S_2$ 325.40	55.36 55.28	3.41 3.23	21.52 21.52	3350, 3240, 3190 ($3NH_2$), 3050 (CH-arom.), 2220 (CN)	7.80-7.40 (m, 5H, arom.), 6.30-6.00 (br, 4H, $2NH_2$), 4.50-4.20 (br, 2H, NH_2)
11b	81	$C_{21}H_{16}N_6S$ 384.45	65.61 65.55	4.19 4.13	21.86 21.77	3337, 3240, 3200 ($3NH_2$), 3050 (CH-arom.), 2200 (CN)	8.00-7.30 (m, 10H, arom.), 6.30-6.00 (br, 4H, $2NH_2$), 4.60-4.30 (br, 2H, NH_2)
12a	89	$C_{12}H_{11}N_5S_2O_2$ 321.37	44.85 44.88	3.45 3.51	21.79 21.73	3350, 3240, 3190 ($3NH_2$), 3050 (CH-arom.), 2220 (CN), 1710 (C=O)	6.40-6.10 (br, 4H, $2NH_2$), 4.60-4.40 (br, 2H, NH_2), 4.10-3.80 (q, 2H, CH_2), 1.90-1.50 (t, 3H, CH_3)
12b	71	$C_{18}H_{16}N_6SO_2$ 380.42	56.83 56.91	4.24 4.35	22.09 22.19	3350, 3240, 3190 ($3NH_2$), 3050 (CH-arom.), 2220 (CN), 1710 (C=O)	7.90-7.50 (m, 5H, arom.), 6.40-6.20 (br, 4H, $2NH_2$), 4.50-4.20 (br, 2H, NH_2), 4.10-3.80 (q, 2H, CH_2), 2.00-1.70 (t, 3H, CH_3)

[a]Satisfactory microanalysis obtained: C ±0.4, H ±0.4, N ±0.3%.
[b]Measured on a Nicolet 710 FT-IR Spectrometer.
[c]Measured on Varian EM 360A Spectrometer using TMS as internal standard.

Moreover, 2-aminoprop-1-ene-1,1,3-tricarbonitrile reacted with a variety of cyano containing active methylene compounds including malononitrile, benzyl cyanide or ethylcyanoacetate under PTC conditions and afforded the corresponding thiopyrano(2,3-b)pyridine **10a–12a** or pyrido(2,3-b)pyridine **10b–12b** derivatives (Scheme 4). The analytical and spectral data of the new compounds are listed in Tables I and II.



SCHEME 4

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