SHORT PAPER

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Condensation of α-cyanocinnamonitriles with 6-bromo-2-naphthol: synthesis of pyrano [2,3-*d*]pyrimidine and pyrano[3,2-*e*] [1,2,4]triazolo[2,3-*c*]pyrimidine derivatives†

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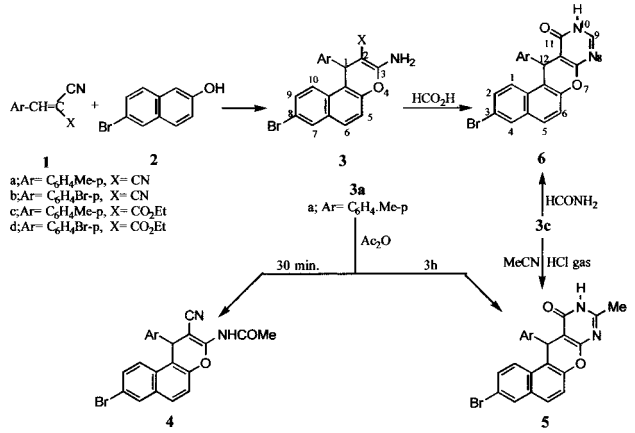
Naphthopyrans are synthesized by the reaction of cinnamonitriles with 6-bromo-2-naphthol; polysubstituted naphthopyrimidines and naphthopyranotriazolopyrimidines are also prepared.

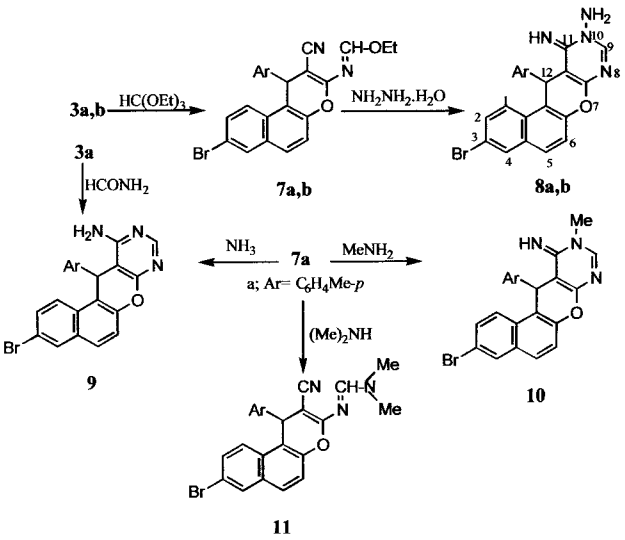
The considerable biological and medicinal activity of fused 4*H*-pyran has stimulated much research in this field.[1–3] In continuation of our previous work[4–6] on the synthesis of fused pyrans using enaminonitriles, we report here the synthesis of a variety of new heterocyclic compounds. Thus, condensation of various substituted α-cyanocinnamonitriles **1a–d** with 6-bromo-2-naphthol **2** in ethanolic piperidine afford 1:1 adducts.[4–8] Structure **3** (Scheme 1) was established on the basis of the ^{1}H NMR spectra, which showed 1-H at δ 5.38 **(3a)** and at δ 5.48 ppm **(3d)**. The increased chemical shift for this signal, compared to the expected value (δ 4.0–5.0 ppm) for such protons, can be attributed to the deshielding effect of the diamagnetic current of the naphthyl, aryl and allylic π-electrons.[8–10] The UV spectrum of **3b** and **3d** revealed a weak shoulder,[6,11] characteristic for 4*H*-pyran, at $\lambda_{max.}$ (CH_3COCH_3) 275 (log ε 2.84) and 275 nm (log ε 2.83) respectively.



Scheme 1

Interaction of 3-amino-8-bromo-1-(*p*-tolyl)-1*H*-naphtho[2,1-*b*]pyran-2-carbonitrile **3a** with acetic anhydride for 30 min afforded the *N*-acetyl derivative **4**, while heating of **3a** with acetic anhydride under reflux for 3h afforded the naphthopyranopyrimidin-11-one derivative **5**. Structure **5** is supported by an independent synthesis of the same product from **3c** and acetonitrile in the presence of HCl gas[12] (Scheme 1). Treatment of **3a** with formic acid gave the naphthopyrimidin-11-one derivative **6**. The structure of **6** was supported by an independent synthesis from **3c** and formamide (Scheme 1). Structures **4-6** were established by spectral data and analogy with our previous work.[4,6]

Treatment of **3a,b** with triethyl orthoformate in acetic anhydride at reflux gave the corresponding ethoxymethyleneamino derivatives **7a,b** (Scheme 2). Hydrazinolysis of **7a,b** in ethanol at room temperature afforded the imino derivatives **8a,b** (Scheme 2). Ammonolysis of **7a** in methanol at room temperature afforded the pyrimidine derivative **9**, the structure of which was supported by its independent synthesis from **3a** and formamide (Scheme 2). Reaction of **7a** with methylamine yielded the pyrimidine derivative **10**, while with dimethylamine the open-chain product **11** was obtained (Scheme 2).



Scheme 2

Interaction of **8a** with triethyl orthoformate afforded 11-bromo-14-(*p*-tolyl)-14*H*-naphtho-[1′,2′:5,6]pyrano[3,2-*e*][1,2,4]triazolo[2,3-*c*]pyrimidine **12a** (Scheme 3), while with acetyl chloride and ethyl cyanoacetate at reflux the corresponding 2-methyl **12b** and 2-acetonitrile **12c** derivative respectively were formed. Reaction of **8a** with diethyl oxalate and benzoyl chloride at reflux afforded the corresponding 2-carboxylate **12d** and 2-phenyl **12e** derivatives respectively, while methyl or ethyl chloroformate in dry benzene afforded the 1:1 adduct **13** (Scheme 3). Structures **7**–**13** were established by spectral data and analogy with our previous work.[4–6]

Instead of the expected formation of the triazolopyrimidine derivative[13] **12e**, the reaction of **8a** with benzaldehyde in dioxan/piperidine gave the dihydrotriazolopyrimidine derivative **14** (Scheme 3). The proposed structure for **14** was supported by TLC and spectral data.

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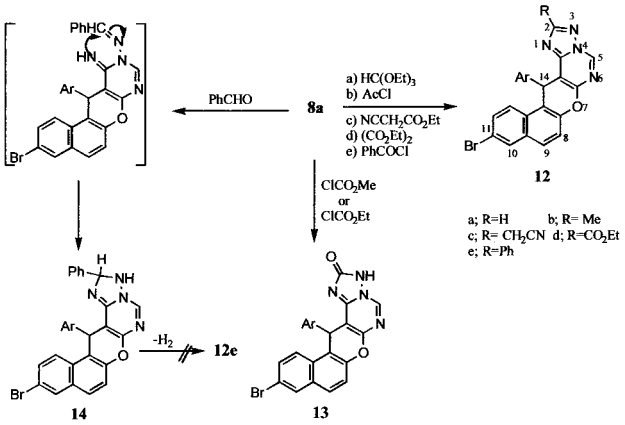
† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*



Scheme 3

Experimental

Mps are uncorrected. Elemental analyses were carried out in the Microanalytical Laboratories of the Faculty of Science, Cairo University. IR spectra (KBr) were measured on a FT IR/5300 spectrometer. Ultraviolet spectra were recorded on Perkin Elmer Lambda-3B UV–visible spectrophotometer. ^{1}H NMR spectra on Varian Mercury (300 MHz) spectrometer and mass spectra on a Shimadzu GC–MS–QP 1000 EX spectrometer.

*Reaction of **1a–d** with 6-bromo-2-naphthol:* A solution of **1** (0.01 mol) in ethanol (30 ml) was treated with 6-bromo-2-naphthol **2** (0.01 mol) and piperidine (0.5 ml). The reaction mixture was heated until complete precipitation (reaction times: 15 min. for **1a,b;** 120 min for **1c,d**). The solid product which formed was collected by filtration and recrystallized from a suitable solvent to give **3a-d** (70-80% yield) (Table 1). **3a**: $\nu_{max.}$/cm^{-1} 3325, 3283 (NH_2), 2924, 2851 (CH stretching), 2176 (CN); δ_H ([$^2H_6$]DMSO) 7.25–7.85 (9H,m, arom.), 6.89 (2H,br, NH_2), 5.38 (1H,s, pyran CH), 2.34 (3H,s, CH_3). **3b**: $\nu_{max.}$/cm^{-1} 3468, 3319 (NH_2), 2193 (CN). **3d**: ν_{max}/cm^{-1} 3485, 3325 (NH_2), 2980, 2936, 2891 (CH stretching), 1684 (CO ester); δ_H ([$^2H_6$]DMSO) 7.22–8.20 (9H,m, arom.), 7.19 (2H,br, NH_2), 5.48 (1H,s, pyran CH), 4.10 (2H,q, CH_2, *J*=7.2 Hz) and 1.26 (3H,t, CH_3, *J*=7.2 Hz).

2-Acetylamino-7-bromo-4-(p-tolyl)-4H-naphtho[2,1-b]pyran-3-carbonitrile **(4)**: A solution of **3a** (0.01 mol) in acetic anhydride (20 ml) was heated under reflux for 15 min to give the N-acetyl derivatives **4** (81% yield) (Table 1), $\nu_{max.}$/cm^{-1} 3200 (NH), 3047, 2927 (CH stretching), 2206 (CN), 1707 (CO acetyl); δ_H ([$^2H_6$]DMSO) 11.15 (1H,br, NH), 7.13-8.26 (9H,m, arom.), 5.59 (1H,s, pyran CH), 2.52 (3H,s, $COCH_3$) and 2.23 (3H,s, CH_3).

3-Bromo-9-methyl-12-(p-tolyl)-10,11-dihydro-12H-naphtho[1´,2´:5,6]pyrano[2,3-d]pyrimidin-11-one **(5)**: **(a)** A solution of **3a** (0.01 mol) in acetic anhydride (20 ml) was heated under reflux for 3h to give **5** (86% yield) (Table 1), $\nu_{max.}$/cm^{-1} 3260 (NH), 3001, 2850 (CH stretching) and 1651 (CO).

(b) A stream of dry HCl gas was passed through a mixture of **3c** (0.01 mol) and acetonitrile (30 ml) for 4–6h. The reaction mixture was poured into ice-water and basified with 10% ammonium hydroxide solution to give **5** (68% yield) (Table 1).

3-Bromo-12-(p-tolyl)-10,11-dihydro-12H-naphtho[1´,2´:5,6]pyrano[2,3-d]pyrimidin-11-one **(6)**: **(a)** A solution of **3a** (0.01 mol) in formic acid (20 ml) was heated under reflux for 6h. to give **6** (67% yield) (Table 1),. $\nu_{max.}$/cm^{-1} 3400 (NH), 3035, 2995 (CH stretching) and 1675 (CO).

(b) A solution of **3c** (0.01 mol) in formamide (20 ml) was heated under reflux for 6h. to give **6** (73% yield) (Table 1).

4-Aryl-7-bromo-2-ethoxymethylideneamino-4H-naphtho[2,1-b]pyran-3-carbonitrile **(7a,b)**: A mixture of **3a,b** (0.01 mol), triethyl orthoformate (0.01 mol) and acetic anhydride (20 ml) was refluxed for 5h to give **7a,b** (75–82% yield) (Table 1). **7a:** ν_{max}/cm^{-1} 2980, 2922, 2860 (CH stretching), 2207 (CN); δ_H ([$^2H_6$]DMSO) 8.71 (1H,s, CH), 7.11–8.21(9H,m, arom.), 5.52(1H,s, pyran CH), 4.33(2H,q, CH_2, *J*=6.9 Hz), 2.21 (3H,s, CH_3), 1.32 (3H,t, CH_3, *J*=6.9 Hz). **7b:** $\nu_{max.}$/cm^{-1} 2986, 2937, 2855 (CH stretching), 2206 (CN); δ_H ([$^2H_6$]DMSO) 8.73 (1H,s, CH), 7.22–8.23(9H,m, arom.), 5.65 (1H,s, pyran CH), 4.34 (2H,q, CH_2, *J*= 6.9 Hz) and 1.32 (3H,t, CH_3, *J*=6.9 Hz).

10-Amino-12-aryl-3-bromo-11-imino-10,11-dihydro-12H-naphtho[1´,2´:5,6]pyrano[2,3-d]-pyrimidine **(8a,b)**: A solution of **7a,b** (0.01 mol) and hydrazine hydrate (99%, 5 ml) in ethanol (50 ml) was stirred for 45 min to give **8a,b** (85–87% yield) (Table 1). **8a:** $\nu_{max.}$/cm^{-1} 3375, 3300 (NH_2), 3161 (NH); *m/z* 434/432 (M^+, 25/26%), 418/416 (99/100), 342/340 (15/17), 272/270 (4/4), 246/244 (5/6), 165 (14), 111 (7), 73 (9). **8b:** $\nu_{max.}$/cm^{-1} 3354, 3325 (NH_2) and 3168 (NH).

11-Amino-3-bromo-12-(p-tolyl)-12H-naphtho[1´,2´:5,6]pyrano[2,3-d]pyrimidine **(9)**: **(a)** Compound **9** was prepared from **7a** (0.01 mol) and NH_3 gas according to the procedure described for **8**; (88% yield) (Table 1), $\nu_{max.}$/cm^{-1} 3431, 3319 (NH_2) and 1649 (C=N).

(b) Compound **9** was prepared from **3a** (0.01 mol) and formamide (0.01 mol) according to the procedure described for **6** (method b) (65% yield) (Table 1).

3-Bromo-10-methyl-11-imino-12(p-tolyl)-10,11-dihydro-12H-naphtho[1´,2´:5,6]pyrano[2,3-d]-pyrimidine **(10)**: Compound **10** was prepared from **7a** (0.01 mol) and methylamine (0.01 mol) according to the procedure described for **8** (83% yield) (Table 1), $\nu_{max.}$/cm^{-1} 3342 (NH), 3020, 2918, 2876 (CH stretching), 1645 (C=N), δ_H ([$^2H_6$]DMSO) 8.21 (1H,s, pyrimidine CH), 7.03-8.10 (9H,m, arom.), 7.00 (1H,br, NH), 5.88 (1H,s, pyran CH), 3.35 (3H,s, N–CH_3) and 2.15 (3H,s, CH_3).

7-Bromo-2-dimethylaminomethylideneamino-4-(p-tolyl)-4H-naphtho[2,1-b]pyran-3-carbonitrile **(11)**: Compound **11** was prepared from **7a** (0.01 mol) and dimethylamine (0.01 mol) according to the procedure described for **8** (87% yield) (Table 1), $\nu_{max.}$/cm^{-1} 2920, 2855, 2814 (CH stretching), 2195 (CN), δ_H ([$^2H_6$]DMSO) 8.48 (1H,s, =CH), 7.01–8.18 (9H,m, arom.), 5.39 (1H,s, pyran CH), 3.17 (3H,s, NCH_3), 3.01 (3H,s, NCH_3) and 2.22 (3H,s, CH_3).

11-Bromo-14-(p-tolyl)-14H-naphtho[1´,2´:5,6]pyrano[3,2-e][1,2,4]triazolo[2,3-c]pyrimidine **(12a)**: A solution of **8a** (0.01 mol) and triethyl orthoformate (0.01 mol) in dry benzene was refluxed for 6h to give **12a** (79% yield) (Table 1), *m/z* 444/442 (M^+, 23/21%), 353/351 (95/100), 299/297 (6/6), 218 (7), 192 (1), 165 (3), 112 (7) and 77 (9).

11-Bromo-2-methyl-14-(p-tolyl)-14H-naphtho[1´,2´:5,6]pyrano[3,2-e][1,2,4]triazolo[2,3-c]-pyrimidine **(12b)**: Compound **12b** was prepared from **8a** (0.01 mol) and acetyl chloride (0.01 mol) according to the procedure described for **12a** (84% yield) (Table 1), $\nu_{max.}$/cm^{-1} 3060, 2980, 2950 (CH-stretching), 1643 (C=N), δ_H ([$^2H_6$]DMSO) 8.74 (1H,s, pyrimidine CH), 7.06–8.20 (9H,m, arom.), 6.49 (1H,s, pyran CH), 3.57(3H,s,triazolo CH_3) and 2.16 (3H,s, CH_3).

11-Bromo-14-(p-tolyl)-14H-naphtho[1´,2´:5,6]pyrano[3,2-e][1,2,4]triazolo[2,3-c]pyrimidin-2-acetonitrile **(12c)**: A mixture of **8a** (0.01 mol) and ethyl cyanoacetate (0.01 mol) and absolute ethanol (20 ml) was refluxed for 6h to give **12c** (65% yield) (Table 1), $\nu_{max.}$/cm^{-1} 3059, 3030, 2930, 2876 (CH stretching) and 2255 (CN).

Ethyl 11-bromo-14-(p-tolyl)-14H-naphtho[1´,2´:5,6]pyrano[3,2-

Table 1 Characterization data for newly synthesized compounds

Compound No.	Mp (T/°C)[a]	Molecular formula	Found (required) (%) C	H
3a	215[b]	$C_{21}H_{15}BrN_2O$	64.4 (64.62)	3.6 (3.85)
3b	250[b]	$C_{20}H_{12}Br_2N_2O$	52.7 (52.86)	2.5 (2.64)
3c	185[b]	$C_{23}H_{20}BrNO_3$	63.3 (63.16)	4.4 (4.58)
3d	165[b]	$C_{22}H_{17}Br_2NO_3$	52.8 (52.69)	3.5 (3.39)
4	255	$C_{23}H_{17}BrN_2O_2$	63.7 (63.89)	3.8 (3.94)
5	310	$C_{23}H_{17}BrN_2O_2$	63.9 (63.89)	4.0 (3.94)
6	140[b]	$C_{22}H_{15}BrN_2O_2$	63.0 (63.16)	3.3 (3.59)
7a	178	$C_{24}H_{19}BrN_2O_2$	64.7 (64.57)	4.4 (4.26)
7b	190	$C_{23}H_{16}Br_2N_2O_2$	51.1 (51.30)	2.7 (2.97)
8a	250	$C_{22}H_{17}BrN_4O$	61.0 (61.11)	3.8 (3.94)
8b	265	$C_{21}H_{14}Br_2N_4O$	50.9 (50.81)	3.0 (2.82)
9	297	$C_{22}H_{16}BrN_3O$	63.2 (63.31)	3.6 (3.84)
10	278	$C_{23}H_{18}BrN_3O$	64.0 (64.04)	4.0 (4.18)
11	248	$C_{24}H_{20}BrN_3O$	64.9 (64.72)	4.5 (4.49)
12a	310[c]	$C_{23}H_{15}BrN_4O$	62.4 (62.44)	3.4 (3.39)
12b	285[c]	$C_{24}H_{15}BrN_4O$	63.0 (63.16)	3.6 (3.73)
12c	287	$C_{25}H_{16}BrN_5O$	62.3 (62.37)	3.4 (3.33)
12d	215	$C_{26}H_{19}BrN_4O_3$	60.6 (60.70)	3.7 (3.70)
12e	290[d]	$C_{29}H_{19}BrN_4O$	67.2 (67.18)	3.7 (3.67)
13	292[c]	$C_{23}H_{15}BrN_4O_2$	60.1 (60.26)	3.1 (3.28)
14	295[d]	$C_{29}H_{21}BrN_4O$	67.0 (66.92)	4.1 (4.04)

[a]From benzene unless indicated otherwise. [b]From ethanol. [c]From DMF [d]From dioxan

e][1,2,4]triazolo[2,3-c]pyrimidine-2-carboxylate **(12d)**: Compound **12d** was prepared from **8a** (0.01 mol) and ethyl oxalate (0.01 mol) according to the procedure described for **12c**, (80% yield) (Table 1), $\nu_{max.}$/cm^{-1} 3111, 2990, 2891 (CH stretching), 1718 (CO), 1618 (C=N), δ_H ([$^2H_6$]DMSO) 8.74 (1H,s, pyrimidine CH), 7.06–8.31 (3H,m, arom.), 6.33 (1H,s, pyran CH), 3.99 (2H,q,CH_2, *J*= 6.9 Hz), 2.17 (3H,s,CH_3), 1.10 (3H,t,CH_3, *J*= 6.9 Hz), *m/z* 516/514 (M^+, 1/1%), 420/ 418 (49/54), 328/326 (86/100), 193 (16), 166 (1), 140 (2), 112 (3) and 65 (11).

11-Bromo-2-phenyl-14-(p-tolyl)-14H-naphtho[1´,2´:5,6] pyrano[3,2-e][1,2,4]triazolo[2,3-c]pyrimidine **(12e)**: Compound **12e** was prepared from **8a** (0.01 mol) and benzoyl chloride (0.01 mol) according to the procedure described for **8a**, (62% yield) (Table 1), $\nu_{max.}$/cm^{-1} 3005 (CH-stretching), 1633 (C=N), δ_H ([$^2H_6$]DMSO) 9.67 (1H,s, pyrimidine CH), 7.03–8.31 (14H,m, arom.), 6.37 (1H,s, pyran CH) and 2.13 (3H,s, CH_3).

11-Bromo-2,3-dihydro-2-oxo-14-(p-tolyl)-14H-naphtho[1´,2´:5,6] pyrano[3,2-e][1,2,4]triazolo-[2,3-c]pyrimidine **(13)**: Compound **13** was prepared from **8a** (0.01 mol) and methyl chloroformate or ethyl chloroformate (0.01 mol) according to the procedure described for **12a**, (74% yield) (Table 1),$\nu_{max.}$/cm^{-1} 3362 (NH), 2049, 2989, 2856 (CH stretching) and 1647 (CO).

11-Bromo-2,3-dihydro-2-phenyl-14-(p-tolyl)-14H-naphtho[1´,2´:5,6]pyrano[3,2-e][1,2,4]triazolo-[2,3-c]pyrimidine **(14)**: A mixture of **8a** (0.01 mol), benzaldehyde (0.01 mol), dioxan (20 ml) and piperidine (0.5 ml) was refluxed for 16h to give **14** (85% yield) (Table 1), $\nu_{max.}$/cm^{-1} 3188 (NH), 3028, 2920, 2891, 2855 (CH stretching), δ_H ([$^2H_6$]DMSO) 11.17 (1H, br, NH), 8.39 (1H,s, pyrimidine CH), 7.00-8.29 (14H,m, arom.), 6.68 (1H,s, pyran CH), 3.58 (1H,s, triazoline CH), 2.12 (3H,s, CH_3); *m/z* 522/520 (M^+, 13/12%), 418/416 (78/100), 391/389 (15/19), 300/298 (13/14), 218 (5), 191 (1), 164 (7), 135 (4) and 72 (2).

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