13. Schwarz, J. S. P., *J. Org. Chem. 37*, 2906 (1972).
14. Curtin, D. Y. and Miller, L. L., *J. Am. Chem. Soc. 89*, 637 (1967).
15. Lakhanpal Sunita, Rao, G. C., and Misra, B. N., *Collect. Czech. Chem. Commun. 57*, 540 (1992).
16. Jeanrenaud, A., *Chem. Ber. 22*, 1272 (1992).
17. Cooley, J. H., Bills, W. D., and Trockmorton, J. R., *J. Org. Chem. 25*, 1734 (1960).
18. Kornblum, H., Smiley, R. A., Blackwood, R. K., and Iffland Don, C., *J. Am. Chem. Soc. 77*, 6269 (1955).
19. Willams, D. H. and Flemming, I., *Spectroscopic Methods in Organic Chemistry,* p. 61. McGraw-Hill, London, 1966.
20. McCormack, M. T., *Ph.D. Thesis.* National University of Ireland, Dublin, 1976.

One-Pot Base-Catalyzed Condensation Reactions of Activated Nitriles and 2-Hydroxy-1-naphthalenecarbaldehyde with Different Ketones

A. A. FADDA*, M. T. ZIMAITY, M. M. GIRGES, Ed. BIEHL, and H. M. KHALID

Department of Chemistry, Mansoura Faculty of Science, Mansoura University, 355 16 Mansoura, Egypt

Received 1 September 1993

Several new naphtho[1′,2′:5,6]pyrano[2,3,4-*de*](pyrido[2,3-*d*]pyrimidine), naphtho[1′,2′:5,6]-pyrano[2,3-*d*]pyrimidine, and naphtho[2,1-*b*]pyran derivatives were prepared by a one-pot condensation reaction of malononitrile and 2-hydroxy-1-naphthalenecarbaldehyde (*I*) in the presence of different kinds of ketones and ammonium acetate. The effect of solvents and different basic catalysts on the reaction of *I* with cyanoacetamide or ethyl cyanoacetate in the presence of different ketones was also investigated.

Previous reports have shown that pyran derivatives possess pronounced biological properties [1]. On the other hand, substituted pyridines showed acaricidal, insecticidal, and herbicidal activities [2]. Moreover, pyrimidines are important analgesic and anti-inflammatory [3, 4] agents. So, compounds having a combination of naphthopyran with pyridine and/or pyrimidine moieties can be expected to possess marked biological properties. It has been reported that malononitrile condenses with cresotaldehyde (3-methyl- or 4-methyl-2-hydroxybenzaldehyde) in the presence of ammonium acetate to give the substituted benzopyran-3-carbonitrile derivatives [5]. When methyl ethyl ketone is added to the reaction mixture, the substituted nicotinonitrile derivatives are formed.

Thus, in an extension to our previous work [6—8] for synthesis of novel heterocyclic fused-ring systems of potential activity, we report herein on the synthesis of some new heterocycles that incorporate both naphthopyran, pyridine and/or pyrimidine moieties *via* one-pot base-catalyzed condensation of 2-hydroxy-1-naphthalenecarbaldehyde (*I*) with activated nitriles and different ketones. The produced compounds might have extended and/or improved biological activities.

*The author to whom the correspondence should be addressed.

EXPERIMENTAL

Melting points are not corrected. The IR spectra (KBr) of the prepared compounds were measured on a Pye—Unicam SP 2000 spectrophotometer. EIMS (70 EV) were recorded on GC—MS apparatus, QP-1000 EX (Schimadzye, Japan).

Derivatives *II—XV*

Characterization data for the prepared compounds are given in Table 1.

Method A — Reaction of Activated Nitriles with 2-Hydroxy-1-naphthalenecarbaldehyde (I)

A mixture of compound *I* (0.03 mol), activated nitrile (0.03 mol), and ammonium acetate (0.05 mol) or triethylamine (2—3 drops) in ethanol or glacial ace-

Table 1. Characterization Data of the Prepared Compounds

Compound	Formula	w_i(calc.)/% w_i(found)/%		Yield	M.p.	$M_r(M^+)$
		C	H	%	°C	
II	$C_{14}H_8N_2O$	76.4 76.1	3.6 3.5	85	280	220
III	$C_{20}H_{10}N_6O$	68.6 68.0	2.9 3.3	73	240	350
IV	$C_{25}H_{14}N_4O$	77.7 77.2	3.6 3.5	74	270	386
V	$C_{17}H_{10}N_4O$	71.3 70.9	3.5 3.4	80	220	286
VII	$C_{22}H_{14}N_4O$	75.4 74.8	4.0 4.1	82	150	350
VIII	$C_{23}H_{16}N_4O$	75.8 75.7	4.4 4.5	74	190	364
IX	$C_{14}H_8N_2O$	76.4 76.2	3.6 3.1	81	135	220
X	$C_{14}H_{10}N_2O_2$	70.6 70.3	4.2 4.0	78	220	238
XI	$C_{19}H_{14}N_2O_2$	75.5 74.9	4.6 5.0	70	285	302
XII	$C_{19}H_{14}N_2O_2$	75.5 75.0	4.6 5.0	82	210	302
XIII	$C_{14}H_7NO_2$	76.0 75.5	3.2 3.1	80	285	221
XIV	$C_{16}H_{13}NO_3$	71.9 71.5	4.9 4.6	64	180	267
XV	$C_{19}H_{13}NO_3$	75.2 74.9	4.3 4.5	73	290	303
XVI	$C_{16}H_{12}O_4$	71.6 71.2	4.5 4.3	70	118	268

tic acid (20—25 cm^3) was refluxed for 0.5—2 h (monitored by TLC). The so formed coloured products were filtered while hot, washed well with hot ethanol, dried and recrystallized from benzene or methanol.

Method B — Reaction of Activated Nitriles with 2-Hydroxy-1-naphthalenecarbaldehyde and Acyclic or Cyclic Ketones

A mixture of compound *I* (0.03 mol), activated nitrile (0.03 mol), ketone (0.03 mol), and ammonium acetate (0.05 mol) or triethylamine (2—3 drops) in ethanol or glacial acetic acid (20—25 cm^3) was refluxed for 15—120 min (monitored by TLC). Yellow to orange precipitates were formed during refluxation. The so formed products were collected by filtration, washed well with hot ethanol, dried and recrystallized from benzene or methanol.

Isolation of pure substances from the mixed products, that were formed by methods *A* and *B* (monitored by TLC), was achieved by means of fractional crystallization using benzene or methanol.

Method C — Reaction of IX, X, and XIV with Cyclopentanone Yielding XI, XII, and XV

A mixture of the naphthopyridine derivative *IX* or the naphthopyran derivative *X* or *XIV* (0.01 mol in each case), cyclopentanone (0.01 mol), and ammonium acetate (0.15 mol) in ethanol (20 cm^3) was refluxed for 2 h. The precipitated coloured product was filtered off, washed well with hot ethanol, dried and recrystallized from benzene. The produced cyclopentanopyridonaphthopyran derivative *XII* and cyclopentanopyranonaphthopyran derivative *XV* showed no depression in their melting points when admixed with authentic samples that were prepared by the method *B*.

RESULTS AND DISCUSSION

Condensation of the 2-hydroxy-1-naphthalenecarbaldehyde (*I*) with malononitrile in equimolar ratio and in the presence of a slight excess of ammonium acetate afforded the 2-cyano-3-iminonaphtho-[2,1-*b*]pyran (*II*) in good yield.

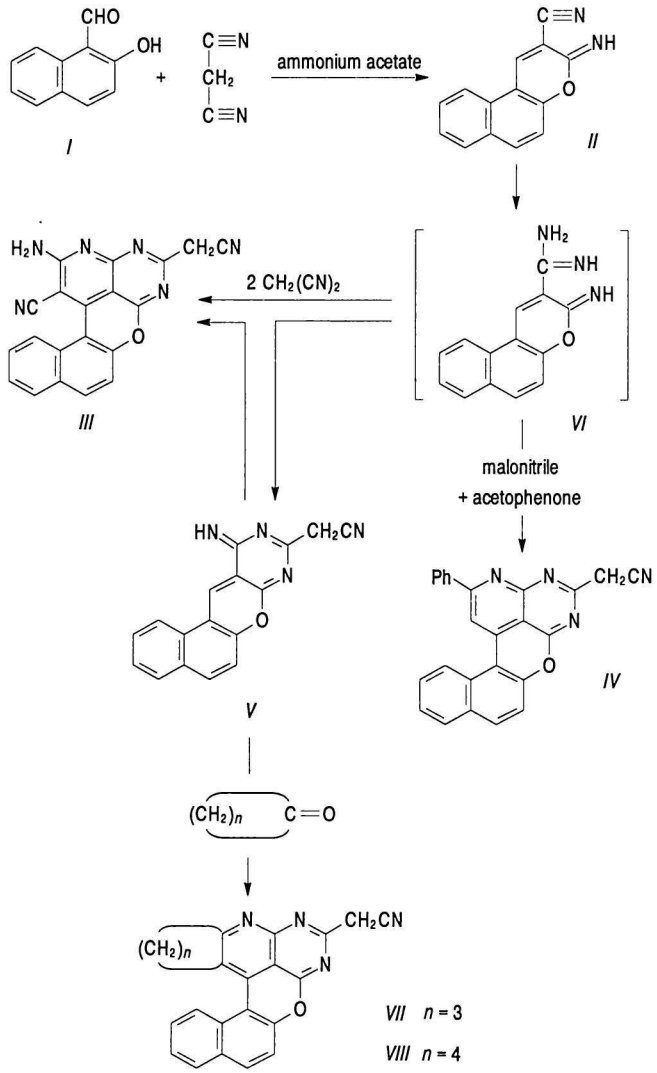
When *I* was heated with an excess of malononitrile, 12-amino-11-cyano-2-cyanomethylnaphtho[1′,2′: 5,6]pyrano[2,3,4-*de*](pyrido[2,3-*d*]pyrimidine) (*III*) was formed as the main product.

On the other hand, when this reaction was carried out in the presence of a catalytic amount of triethylamine or piperidine instead of ammonium acetate, compound *II* was formed as the only product.

While the infrared spectrum of compound *II* revealed the presence of C=N, C≡N, and NH absorptions at $\tilde{\nu}$ = 1650 cm^{-1}, 2220 cm^{-1}, and 3150 cm^{-1}, respectively, the IR spectrum of compound *III* showed absorption bands at $\tilde{\nu}$ = 1630 cm^{-1}, 2220 cm^{-1}, and 3410—3450 cm^{-1} that are characteristic of C=N, C≡N, and NH_2 stretching vibrations, respectively.

Refluxing equimolar quantities of a mixture of *I*, malononitrile, and acetophenone for 2 h in the presence of a slight excess of ammonium acetate yielded a mixture of 9—12 % of compound *III*, 17—20 % of 2-cyanomethyl-12-phenylnaphtho[1′,2′: 5,6]pyrano-[2,3,4-*de*](pyrido[2,3-*d*]pyrimidine) (*IV*), and 12 % of 3-cyanomethyl-1-iminonaphtho[1′,2′:5,6]pyrano[2,3-*d*]pyrimidine (*V*), respectively. Minimizing reflux time to only 10—15 min afforded a mixture of *II, IV,* and *V* in 15 %, 10 %, and 7 % yields. All attempts to control this reaction to afford the 1 : 1 adduct were unsuccessful even when limited quantities of malononitrile were used under conditions favourable for monocycloaddition.

Although several isomeric structures seemed possible, structures *III*, *IV*, and *V* were established for the reaction products based on their spectral data. On the other hand, when this reaction was refluxed for short or long time in the presence of triethylamine, compound *II* was formed as the only product. The IR spectrum of *IV* showed absorption bands in the region of $\tilde{\nu}$ = 1630 cm^{-1} and 2220 cm^{-1} assignable



Scheme 1

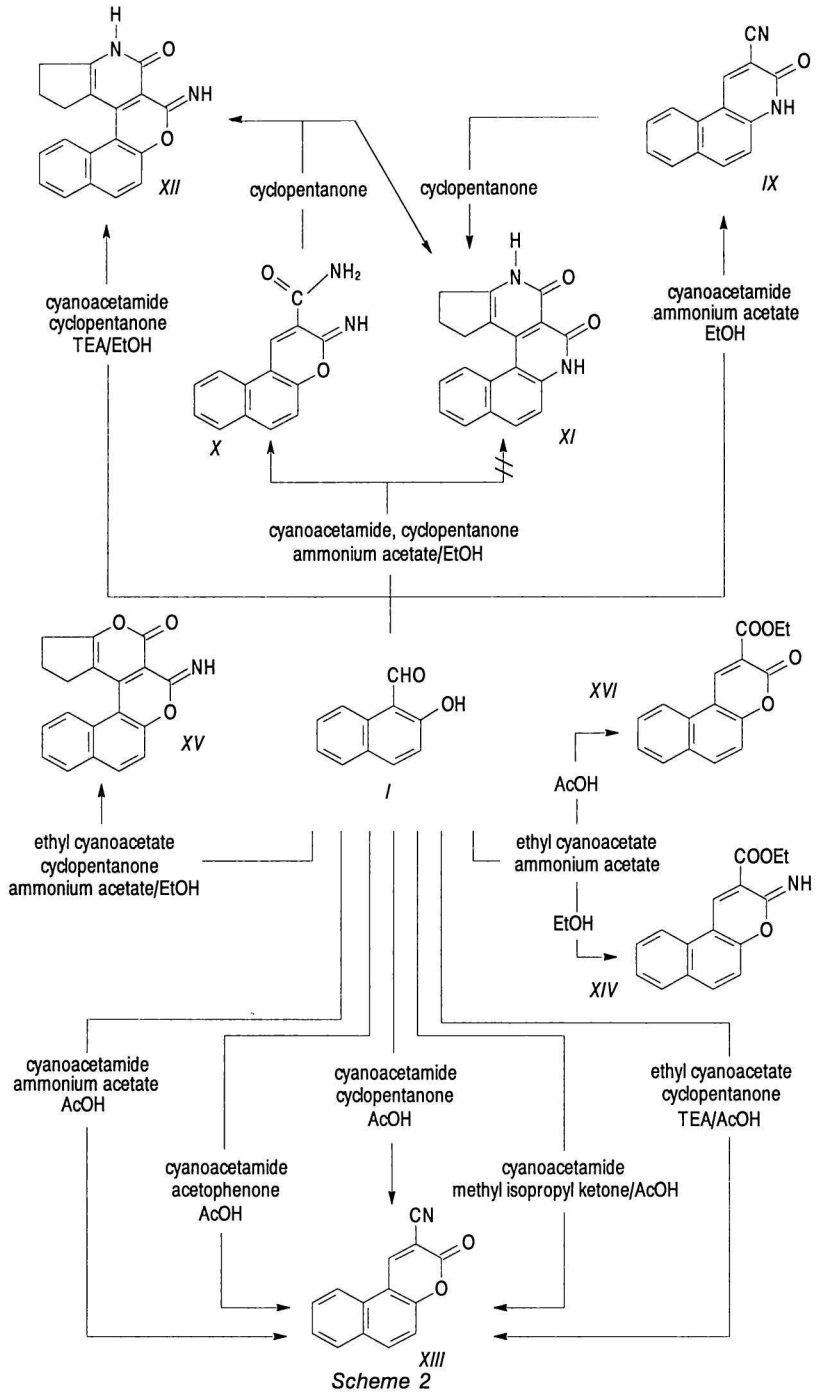
to stretching vibrations of the C=N and C≡N moieties, respectively, meanwhile this spectrum did not show any band in the amino or imino region. For compound *V*, the IR spectrum showed the characteristic bands of *exo* and *endo* C=N, C≡N, and NH groups at $\tilde{\nu}$ = 1630—1650 cm^{-1}, 2220 cm^{-1}, and 3150 cm^{-1}, respectively.

The formation of these products indicates that in many cases the course of the reaction is markedly influenced by the choice of the basic catalyst and/or reaction time. It seems reasonable to assume that the formation of compounds *II*—*V* may be achieved by a process where malononitrile firstly condenses with 2-hydroxy-1-naphthalenecarbaldehyde to give *II*, which in turn is converted to amidinonaphthopyran derivative *VI*. The latter intermediate condenses with the available ketone and then reacts with additional molecule of malononitrile to afford the final product *IV*.

As indicated in Scheme 1, the formation of compound *V* could be achieved *via* addition of malononitrile to the intermediate *VI*. Reaction of *V* with additional molecule of malononitrile afforded compound *III*. Moreover, the product *III* could be also formed *via* reaction of the intermediate *VI* with two molecules of malononitrile.

Indeed when heated with acetophenone and ammonium acetate in ethanol, compound *II* gave product *IV*. When cyclopentanone was used as the ketone reactant, a mixture of *VII* (30 %) and *V* (15 %), respectively, was formed. Reaction with cyclohexanone under similar conditions afforded compound *VIII* as the only product in 35 % yield.

The formation of *VII* and *VIII* was assumed to proceed *via* addition of α-carbon atom of the ketone molecule to the activated double bond in compound *V* followed by cyclocondensation of the produced Michael adduct through elimination of water molecule and finally aromatization of these cyclic structures, under the used reaction condition, to the corresponding isolable end products *VII* and *VIII*, respectively.



Scheme 2

The IR spectra of compounds *VII* and *VIII* showed no absorption bands for amino or imino groups and were very similar to those of compound *IV*.

The behaviour of cyanoacetamide or ethyl cyanoacetate in such condensation reactions was also investigated. It has been found that compound *I* reacts with cyanoacetamide in the presence of ammonium acetate and absolute ethanol to yield 65 % of the naphtho[2,1-*b*]pyridine derivative *IX* as a single product (controlled by TLC) (Scheme 2). The IR spectrum of *IX* showed absorption bands at $\tilde{\nu}$ = 1680 cm^{-1}, 2220 cm^{-1}, and 3150 cm^{-1} attributable to the stretching vibration of carboxamido, cyano, and NH groups, respectively.

Unexpectedly, when compound *I* was allowed to react with a mixture of cyanoacetamide and cyclopentanone in absolute ethanol and in the presence of ammonium acetate it gave the iminonaphthopyranamide *X* instead of the corresponding cyclopentanopyridonaphthopyridine derivative *XI* in good yield.

Using triethylamine instead of ammonium acetate as a catalyst in the above-mentioned reaction, a mixture of the two isomeric products of structures *XI* and *XII* was formed.

Again the formation of these isomeric products is assumed to proceed *via* addition of the cyclopentanone C-2 carbon to the activated double bonds of *IX* and *X* (which are assumed to be formed firstly) followed by cyclization and aromatization of the produced Michael adducts to give the end products *XI* and *XII*, respectively.

Structures *XI* and *XII* were established not only by their analytical and spectral data but also by an independent synthesis *via* reaction of either *IX* or *X* with cyclopentanone and ammonium acetate in absolute ethanol. While IR spectrum of compound *XI* revealed only the characteristic absorption bands for the cyclic secondary amidic linkage at $\tilde{\nu}$ = 1680 cm^{-1} and 3150 cm^{-1}, IR spectrum of *XII* revealed absorption bands nearby $\tilde{\nu}$ = 1650 cm^{-1}, 1680 cm^{-1}, and 3150 cm^{-1} assignable to stretching vibrations of the exocyclic C=N bond, carboxamido and NH functions, respectively.

In spite of the fact that the acid catalysis of Michael addition is rather seldom [9], the above procedure was repeated using glacial acetic acid with a view that the reaction might proceed to the end probably by virtue of the thermodynamically very stable products that would be formed. Unfortunately, when compound *I*, cyanoacetamide, and ammonium acetate were allowed to react with cyclic or acyclic ketones in the presence of acetic acid, they yielded the 2-cyano-3-oxonaphtho[1,2-*b*]pyran (*XIII*) as the only isolable product for which IR spectrum showed two characteristic absorption bands at $\tilde{\nu}$ = 1700 cm^{-1} and 2220 cm^{-1} that might be assigned to the lactonyl-CO and cyano groups, respectively. The formation of *XIII* in such cases confirms that the use of acetic acid as a solvent did not favour any further cycloaddition reaction and consequently the reaction was stopped at the stage of its formation.

The formation of *XIII* has been established by independent synthesis *via* hydrolysis of *II* in a mixture of concentrated hydrochloric acid and ethanol or alternatively, by acetic acid-mediated condensation of compound *I* with cyanoacetamide and ammonium acetate in the absence of any ketone. Replacing cyanoacetamide with ethyl cyanoacetate in the latter reaction afforded the 2-ethoxycarbonyl-3-oxonaphtho[1,2-*b*]pyran (*XVI*) as the only product. IR spectrum for this product revealed two absorption bands at $\tilde{\nu}$ = 1700 cm^{-1} and 1730 cm^{-1} for carbonyl stretching vibration of cyclic and acyclic carbonyl functions, respectively.

On the other hand, when an ethanolic solution of *I* was allowed to react with ethyl cyanoacetate in the presence of ammonium acetate, it afforded the 2-ethoxycarbonyl-3-iminonaphtho[1,2-*b*]pyran (*XIV*).

When cyclopentanone is added to the reaction mixture of compound *I* with ethyl cyanoacetate and ammonium acetate in ethanol, the cyclopentanopyranonaphthopyran derivative *XV* was formed as the only product.

Carrying out the above reaction in the presence of a catalytic amount of triethylamine and glacial acetic acid led to the formation of compound *XIII* as the only isolable product.

Structure *XV* was confirmed chemically by its independent synthesis through the reaction of ethanolic solution of compound *XIV* with cyclopentanone and ammonium acetate.

The procedures described in this contribution were found to be satisfactory for synthesis of interesting new fused-ring systems in good yield.

REFERENCES

1. Oguro, K. and Hashimoto, K., *Jpn. J. Pharmacol. 24,* 227 (1974) and references cited therein.
2. Rigterink, R. H., *U. S.* 3399205 (1968); *Chem. Abstr. 69,* 96483h (1968).
3. Dey, B. B. and Ammalu, K., *Proc. Natl. Inst. Sci. India 6,* 641 (1940); *Chem. Abstr. 36*, 83 (1942).
4. Cooke, G. A. and Houlihan, J., *U.S.* 397886 (1976); *Chem. Abstr. 85,* 177482 (1976).
5. Fadda, A. A. and Metwally, M. A., *Org. Prep. Proc. Int. 17,* 198 (1985).
6. Fadda, A. A. and Hassan, H. M., *Indian J. Chem. 29B,* 1020 (1990).
7. El-Hossini, M. S., Fadda, A. A., and Khodier, M. N., *Indian J. Chem. 30B,* 25 (1991).
8. Fadda, A. A., Hanna, M. A., and Girges, M. M., *Chem. Papers 46,* 244 (1992).
9. Toma, S., *Chem. Listy 74,* 589 (1980).