Application of (2-Cyanoaryl)arylacetonitriles in Cyclization and Annulation Reactions. Preparation of 3-Arylindans, 4-Aryl-3,4-dihydronaphthalenes, 4-Arylisoquinolines, 1-Aminonaphthalenes, and Heterocyclic Analogues

Michael Bech Sommer,*,† Mikael Begtrup,*,‡ and Klaus Peter Bøgesø†

H. Lundbeck A/S, Ottiliavej 7, DK-2500 Copenhagen, Denmark, and Department of Organic Chemistry, Technical University of Denmark, DK-2800 Lyngby, Denmark

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(2-Cyanoaryl)arylacetonitriles, obtained from *o*-halogen-substituted cyanoaromatics and arylacetonitriles may be alkylated with methyl chloroacetate. Subsequent abstraction of the proton adjacent to the ester group followed by attack of the anion at the aromatic cyano group gives rise to annulated 1-aminocyclopentenes by a Dieckmann-type reaction. The homologous esters similarly produce annulated 1-aminocyclohexenes. The generality of this annulation method is demonstrated by preparation of derivatives of 1-amino-1*H*-indene, 4-amino-6*H*-cyclopenta[*b*]thiophene, 5-amino-7*H*-pyrindine, 1-amino-3,4-dihydronaphthalene, and 5-amino-2,9-dihydro-1*H*-cyclopent[*c*]isoquinoline. Hydrolysis and decarboxylation of these compounds leads to ketones as exemplified by synthesis of 3-arylindan-1-ones and 4-aryl-3,4-dihydro-1(2*H*)-naphthalen-1-ones. When treated with hydrogen bromide, the (2-cyanophenyl)phenylacetonitriles cyclize to [3,4]-condensed 3-bromo-5-aryl-6-aminopyridines. Thus, derivatives of isoquinoline, thieno[3,2-*c*]pyridine, and 1,6-naphthyridine were prepared.

In the preceding paper an effective and general synthesis of (2-cyanophenyl)phenylacetonitriles **3** was described.[1] These compounds are useful building blocks for construction of five- and six-membered rings as illustrated by the processes shown in Scheme I. The sequence involves deprotonation, alkylation to give a species (**4**) with a new acidic proton, deprotonation, and condensation with cyclization producing **5**. Due to the repetitive nature of these steps, the total sequence may frequently be run in one pot, which may also include the preparation of the starting material from 2-chlorobenzonitrile and phenylacetonitrile. The sequence is exemplified by the use of (2-cyanophenyl)phenylacetonitriles for preparation of 1-amino-3-arylindenes **5a**, 1-amino-4-aryltetralins **5b**, and 5-amino-9b-phenyl-2,9b-dihydro-1*H*-cyclopent[*c*]isoquinolines **15**, as well as the heterocyclic analogues **21** and **23**. In a similar reaction, (2-cyanophenyl)-2-cyclopentylideneacetonitrile (**18**) has been transformed into the tricyclic 1-aminonaphthalenes (**19**). Under acidic conditions, (2-cyanophenyl)phenylacetonitriles **3** may cyclize directly by condensation between the two cyano groups with formation of **7** as described by Neumeyer et al.[2] The acid-catalyzed cyclization is also exemplified by the preparation of 4-arylisoquinolines **7** and the heterocyclic analogues **24** and **25**.

3-Arylindans. 3-Arylindan-1-ones **10a** are precursors of 1-amino-3-arylindans, which exhibit a series of important pharmacological properties.[3-6] They have been prepared by (i) Lewis acid catalyzed intramolecular acylation of 3,3-diarylpropionic acids or acid chlorides **11**,[6-8] (ii) lithium–halogen exchange of *o*-bromo-3,3-diarylpropionic acids or esters **12** followed by intramolecular addition of the carbanionic center to the carbonyl group,[9,10] or (iii) Lewis acid catalyzed cyclization of chalchones **13**[11-14] (Scheme II). These methods are encumbered with limitations that make many substitution patterns inaccessible. The first procedure proceeds regioselectively only if R is more activating than R′ toward electrophilic aromatic substitution and if R adopts the 3-position with respect to the propionic acid side chain. These conditions are required to ensure that only the 2-position of the R-substituted nucleus reacts in the intramolecular cyclization. Further limitations exist since many substituents do not tolerate the cyclization conditions of procedure i. The *o*-bromo-3,3-diarylpropionic acids **12** used as starting materials in method ii are frequently not readily available. Another complication is that the alkyllithium used in the metalation step is prone to add to the acyl carbon atom to give a ketone that then cyclizes with production of a 1-alkyl-1-hydroxyindan. Finally, many substituents do not tolerate the cyclization conditions of procedure ii. Method iii does not proceed regioselectively when R is situated at the 3-position. Furthermore, the nature of the substituents is subject to the usual restrictions of Friedel–Crafts reactions. None of the three procedures is suitable for preparation of nitrogen heteroaromatic analogues of **10**. Lewis acids deactivate such rings through coordination with their nitrogen atom and alkyllithium may add to nitrogen heteroaromatics.

Most of the limitations of the reported routes to 3-arylindan-1-ones **10a** can be avoided by using (2-cyanophenyl)phenylacetonitriles **3** as key intermediates in the synthesis. The parent (2-cyanophenyl)phenylacetonitrile (**3**, R = R′ = H), generated in situ from 2-chlorobenzonitrile (**1**, R = H) and benzyl cyanide (**2**, R′ = H), was readily alkylated with methyl chloroacetate in the presence of potassium *tert*-butoxide in dimethylformamide. The product **4a** undergoes a spontaneous Dieckmann-type cy-

† H. Lundbeck A/S.
‡ Technical University of Denmark.

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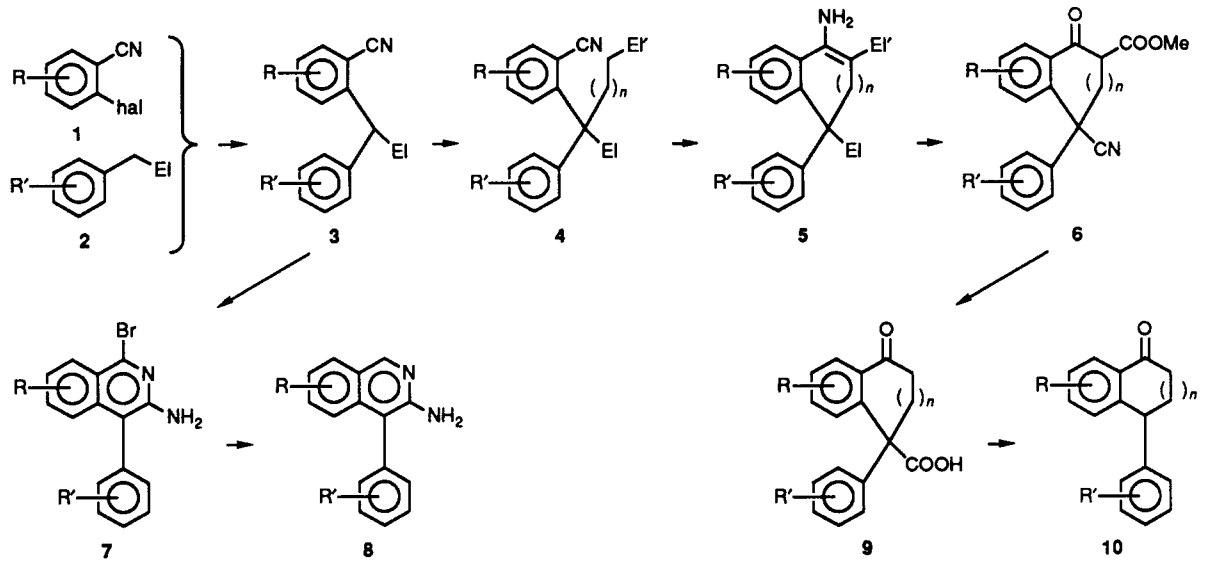
Scheme I[a,b]



[a] **a**, n = 0; **b**, n = 1; **c**, n = 2. [b] El = CN and El′ = COOMe, when not otherwise stated. For R and R′, see Table I and II.

Table I. One-Pot Alkylation and Cyclization of in Situ Prepared (2-Cyanophenyl)phenylacetonitriles 3 into 1-Amino-2-(methoxycarbonyl)-3-cyano-3-aryl-1*H*-indenes 5a

entry	substituted 2-halogenobenzonitrile 1		arylacetonitrile 2, R′	reactn condtns[a]				mp (°C)
	hal	R		temp (°C)	step 1[c] time (h)	Step 2 + 3[d] time (h)	yield of 5a (%)[b]	
1	Cl	H	H	25	1	17	88	190–191
2	Cl	3-Cl	4-F	20–25	1	17[e]	65	208–210
3	F	4-Cl	4-F	15–20	0.5	17	72	236–239
4	F	4-Br	4-F	20	1	17	74	153–155
5	Br	4-CF_3	4-F	20–25	1	17	73	183–185
6	Cl	5-Cl	H	20–30	1.5	17	78	212–214
7	Cl	5-Cl	3-F	20–25	3	20	82	211–213
8	Cl	5-CF_3	4-F	20–25	1[d]	17	83	178–179
9	F	5-OCH_3	4-F	25–30	4	17	72	179–181
10	Cl	6-Cl	H	20–25	0.5[f]	20	73	156–158
11	F	6-F	4-F	15–20	0.5[f]	17	75	127–129
12	Cl	6-OCH_3	4-F	20–30	2.0	17	69	181–185
13	Cl	H	2-F	20–25	2	17	72	208–210
14	Cl	H	4-F	25–30	1	17	85	198–199
15	Cl	H	4-OCH_3	20–25	0.5	17	76	142–144
16	Cl	H	3,4-Cl_2	20–25	2	17	80	198–199
17	Cl	H	3,4-$(OCH_3)_2$	20–25	1[f]	17	79	120–124

[a] Potassium *tert*-butoxide (2 equiv), dimethylformamide, and methyl chloroacetate was used as base, solvent, and alkylating agent, respectively, when not otherwise stated. [b] Overall (three step) yield of isolated, recrystallized material. [c] Step 1 comprises in situ generation of **3** from **1** and **2**. [d] Step 2 comprises alkylation of **3** into **4a** and step 3 comprises cyclization of **4a** into **5a**. [e] Methyl bromoacetate was used in the alkylation step. [f] 1,2-Dimethoxyethane was used as solvent.

clization, producing 1-amino-2-(methoxycarbonyl)-3-cyano-3-phenyl-1*H*-indene (**5a**). The complete sequence from 2-chlorobenzonitrile and benzyl cyanide could be run in one pot in 88% total yield (see Experimental Section). The indene **5a** was transformed to 3-phenylindan-1-one **10a** by hydrolysis in a mixture of water, acetic acid, and sulfuric acid to give the 3-carboxylic acid **9a** followed by decarboxylation by heating in pyridine or *N*-methylpyrrolidone. Substituted (2-cyanoaryl)arylacetonitriles reacted similarly (Table I, entries 2–17). Electron-donating or -attracting substituents at C-5 of the benzonitrile ring other than the nitro group do not influence the reaction significantly. Thus, (2-cyano-4-nitrophenyl)(4-fluorophenyl)acetonitrile (**3**, R = 4-NO_2, R′ = 4-F) could not be alkylated. Presumably, delocalization of the negative charge to the nitro group reduces the nucleophilicity of the carbanion. [The alkylated nitro compound **4a** (R = 4-NO_2, R′ = 4-F), prepared by an independent route by displacement of chlorine of 2-chloro-5-nitrobenzonitrile with the benzylic anion of methyl 3-cyano-3-(4-fluorophenyl)propanoate, cyclized spontaneously to give **5a** (R = 6-NO_2, R′ = 4-F) under the influence of potassium carbonate in dimethylformamide.] Substituents on the second phenyl group have no observable effect on alkylation and cyclization rates. However a bulky substituent at the 3-position seems to reduce the reactivity toward alkylation. Thus, (2-cyano-6-chlorophenyl)(4-fluorophenyl)acetonitrile (**3**, R = 6-Cl, R′ = 4-F) with methyl chloroacetate gave only 23% of the aminoindene **5a** (R = 4-Cl, R′ = 4-F). However, alkylation with the more reactive methyl bromoacetate or with the sterically less demanding chloroacetonitrile took place under mild conditions, producing the aminoindene **5a** (R = 4-Cl, R′ = 4-F, El′ = CN) in excellent yield. The use of chloroacetonitrile instead of methyl chloroacetate also promotes alkylation and cyclization in other cases.

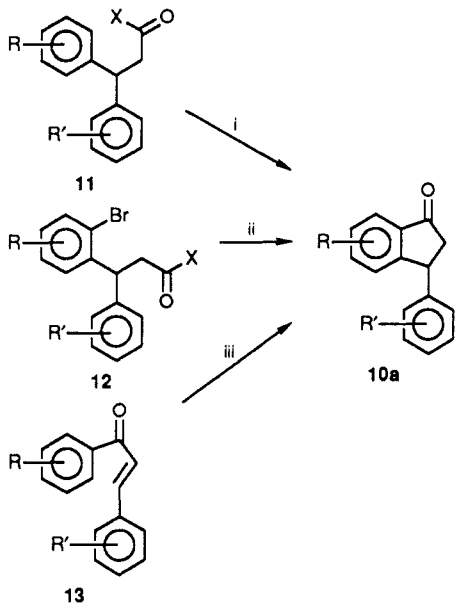
Alkylation of (2-cyano-4-(methylthio)phenyl)(4-fluorophenyl)acetonitrile (**3**, R = 4-SMe, R′ = 4-F) with methyl

Table II. Alkylation and Cyclization of (2-Cyanoaryl)arylacetonitriles into 1-Amino-2-(methoxycarbonyl)-3-cyano-3-aryl-1*H*-indenes 29a

entry	(2-cyanoaryl)arylacetonitrile[a] Ar	Ar′	reactn condtns time (h)/ alkylation[b]	temp (°C)/ cyclization[c]	yield of **29a** (%)[e]	mp (°C)
1	**28**, benzo	3-pyridyl	1/20	17/20	78	231–234
2	benzo	2-thienyl	1/15–20	3/25	77	154–158
3	benzo	3-thienyl	1/25	3/25	76	160–161
4	4-CH_3-benzo	3-thienyl	2/25	1/25	72	182–185
5	4-CF_3-benzo	3-thienyl	1/15–20	4/25	78	204–207
6	benzo	*N*-methylpyrrol-2-yl	3/15–20	2/25	67	210–213
7	**20**[d]		17/10–25	1/20	90	181–183
8	**22**[d]		17/10–25	1/20	78	272–274

[a] Prepared from the corresponding 2-chloroaryl cyanide **26** and arylacetonitrile **27** using 2 equiv of potassium *tert*-butoxide in dimethylformamide,[1] unless otherwise stated. [b] Potassium *tert*-butoxide (1 equiv), dimethylformamide, and methyl chloroacetate was used as base, solvent, and alkylating agent, respectively. [c] Potassium *tert*-butoxide (0.2–1 equiv) and toluene were used as base and solvent, respectively. [d] Potassium carbonate was used in preparing the (2-cyanoaryl)arylacetonitrile. [e] Overall (two step) yield of isolated, recrystallized material.

Scheme II[a]



[a] (i) X = OH; PPA; X = Cl; $AlCl_3$; (ii) X = OH or OR; RLi; (iii) PPA, 136 °C, 30 min.

chloroacetate afforded an isolable alkylation product (**4a**, R = 4-SMe, R′ = 4-F), which could be cyclized by being stirred with catalytic amounts of potassium *tert*-butoxide in *toluene*. Alternative alkylation of the 4-methylthio compound **3** (R = 4-SMe, R′ = 4-F) with chloroacetonitrile using potassium *tert*-butoxide in dimethylformamide gave both alkylation and cyclization to give **5a** (R = 6-SMe, R′ = 4-F) under mild conditions. A series of (2-cyanophenyl)heteroarylacetonitriles behave similarly (Table II, entries 1–6). With methyl chloroacetate they produce isolable alkylation products analogous to **4**, which must be cyclized in a separate step using potassium *tert*-butoxide in *toluene*. The same obtains for (2-cyanoheteroaryl)phenylacetonitriles (Table II, entries 7 and 8). While most amino-1-indenes **5a** can be obtained from 2-halobenzonitriles in a one-pot procedure, preparation of the heteroaromatic analogues 6*H*-cyclopenta[*b*]thiophene **21** and the 7*H*-pyrindine **23** requires three separate steps with different, distinct base and solvent combinations. First, the halogen of the *o*-halo cyano heteroaromatic is displaced with the benzyl cyanide anion generated by using potassium carbonate in dimethylformamide.[1] The subsequent alkylation requires potassium *tert*-butoxide in dimethylformamide. The final cyclization requires potassium *tert*-butoxide in toluene.

Alkylation and cyclization of analogues of (2-cyanophenyl)phenylacetonitriles **3** revealed the latter to be unsurpassed as intermediates in 3-arylindan-1-one synthesis. Indeed, the (2-cyanophenyl)-substituted phenylacetic ester **3** (El = COOMe), generated in situ, reacts with alkylation and cyclization when treated with methyl chloroacetate and potassium *tert*-butoxide in dimethylformamide. However, a part of the ester undergoes alcoholysis under the conditions of alkylation to give the corresponding *tert*-butyl ester. The (2-cyanophenyl)-substituted benzyl phenyl sulfone **3** (El = SO_2Ph) could not be alkylated at all with methyl chloroacetate or methyl bromoacetate. In contrast, the (2-cyanophenyl)phenylthioacetonitrile could be alkylated by methyl chloroacetate; however, the product eliminates thiophenoxide spontaneously with production of (*Z*)- and (*E*)-methyl 3-(2-cyanophenyl)-3-cyanoacrylate.

The new synthesis of 3-arylindan-1-ones from (2-cyanophenyl)phenylacetonitriles is obviously quite general. Particularly, it gives access to 3-arylindan-1-ones with electron-donating substituents in the 3-aryl nucleus. Such compounds are not available by known methodology.

4-Aryl-3,4-dihydro-1(2*H*)-naphthalen-1-ones. Traditionally, 4-aryl-3,4-dihydro-1(2*H*)-naphthalen-1-ones **10b** are obtained by using the same strategy as in the preparation of 3-arylindan-1-ones **10a**.[15] Therefore, the limitations of the accessability of 4-aryl-3,4-dihydro-1(2*H*)-naphthalen-1-ones are similar to those described above for 3-arylindan-1-ones. Most of these limitations may be avoided by using (2-cyanophenyl)phenylacetonitriles **3** as starting materials. Thus, (2-cyanophenyl)(4-fluorophenyl)acetonitrile (**3**, R = H, R′ = 4-F) is alkylated with methyl 3-bromopropanoate in the presence of potassium *tert*-butoxide in dimethylformamide to give **4b** (R = H, R′ = 4-F) in 60% yield. More expedient, alkylation occurs in 91% yield when methyl acrylate is used and with potassium carbonate as the base. The alkylation product **4b** (R = H, R′ = 4-F) cyclized in toluene in the presence of catalytic amounts of potassium *tert*-butoxide, affording the 1-amino-4-(4-fluorophenyl)-3,4-dihydronaphthalene **5b** (R = H, R′ = 4-F) in 85% yield. This compound was hydrolyzed to give the acid (70%) and the acid decarboxylated producing the 4-aryl-3,4-dihydro-1(2*H*)-naphthalen-1-one **10b** (R = H, R′ = 4-F) (85%). All steps in this sequence run parallel with those used for the synthesis of 3-arylindan-1-ones, indicating that the 4-aryl-3,4-dihydro-1(2*H*)-naphthalenone synthesis is as general as the 3-arylindan-1-one synthesis in giving access to 4-aryl-3,4-dihydro-1(2*H*)-naphthalen-1-ones with electron-

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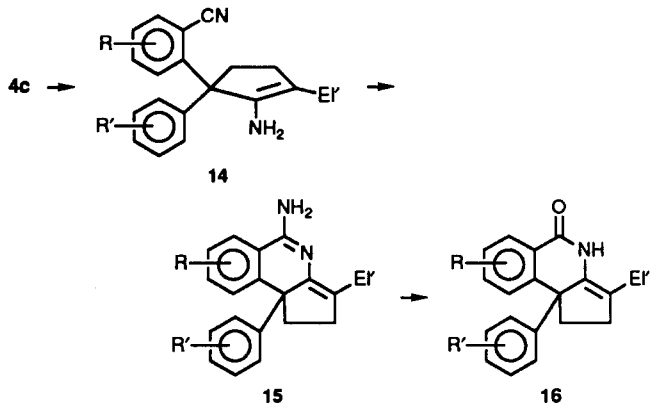
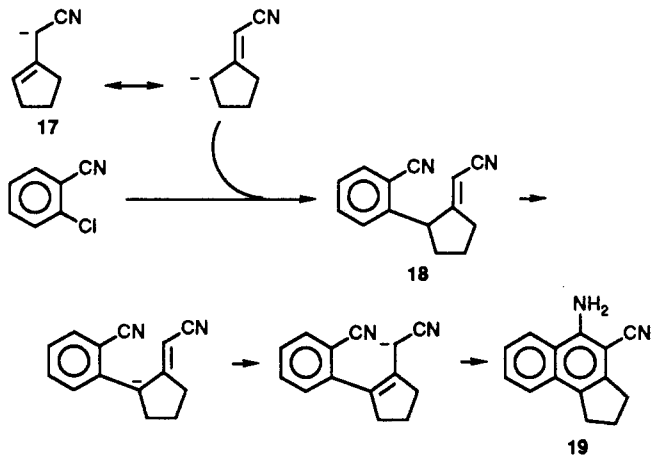
Scheme III



Scheme IV



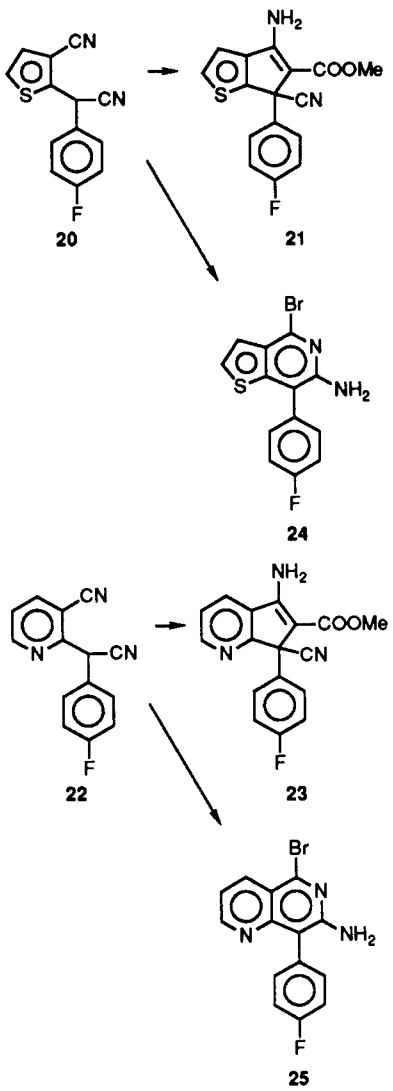
donating substituents in the 4-aryl ring.

9b-Phenyl-2,9-dihydro-1*H*-cyclopent[*c*]isoquinolines. Analogously, alkylation of (2-cyanophenyl)(4-fluorophenyl)acetonitrile **3** (R = H, R′ = H or 4-F) with methyl 4-bromobutyrate gave **4c** (R = H, R′ = H or 4-F), which cyclized upon treatment with potassium *tert*-butoxide in chlorobenzene not to give **5c** but 5-amino-3-(methoxycarbonyl)-9b-phenyl-2,9b-dihydro-1*H*-cyclopent[*c*]isoquinoline (**15**, R = H, R′ = H or 4-F). Most likely, the first cyclization involves the aliphatic cyano group and gives rise to **14** in which the amino group attacks the aromatic cyano group, affording **15** (Scheme III). The identitiy of **15** and its hydrolyzed derivative **16** was ascertained by IR, ^{1}H NMR, ^{13}C NMR, and 2D NMR spectra. All ^{1}H and ^{13}C NMR chemical shifts were close to calculated values (see Experimental Section).

1-Aminonaphthalenes. When 2-chlorobenzonitrile was treated with the (cyclopentenyl)acetonitrile anion (**17**), generated with potassium *tert*-butoxide in dimethylformamide, 5-amino-4-cyano-2,3-dihydro-1*H*-benz[*e*]indene (**19**) was formed in 75% yield. Presumably, an allylic shift precedes nucleophilic displacement of the halogen of the 2-chlorobenzonitrile. Then deprotonation followed by a second allylic shift provides an anion that attacks the aromatic nitrile group with cyclization (Scheme IV). The structure of **19** was elucidated from its ^{1}H and ^{13}C NMR spectra. The position of the substituents was established by nuclear Overhauser experiments, which indicated an effect between an aromatic proton and a CH_2 group, expected only between H-5 and the CH_2 group at C-4 in **19**.

4-Arylisoquinolines. Acid-mediated cyclization of (2-cyanophenyl)phenylacetonitriles **3** to 3-amino-4-arylisoquinolines **7** has been reported in a few instances by Neumeyer et al.[2] The scope of this reaction has been greatly extended by the ready access to substituted (2-cyanophenyl)phenylacetonitriles and their heteroaromatic analogues through the present procedure.[1] Thus, the (3-cyanothien-2-yl)phenylacetonitrile **20** and (3-cyanopyrid-2-yl)(4-fluorophenyl)acetonitrile (**22**), upon treatment with hydrogen bromide in acetic acid, produce high yields of the thieno[3,2-*c*]pyridine **24** and the 1,6-naphthyridine **25**, respectively (Scheme V). Filer et al. have described the deamination of the 1-bromo-3-aminoisoquinolines **7**.[16] Debromination of these intermediates to give **8** is also easily achieved by treatment with sodium borohydride in the presence of palladium as a catalyst (see Experimental Section).

Scheme V



Conclusion

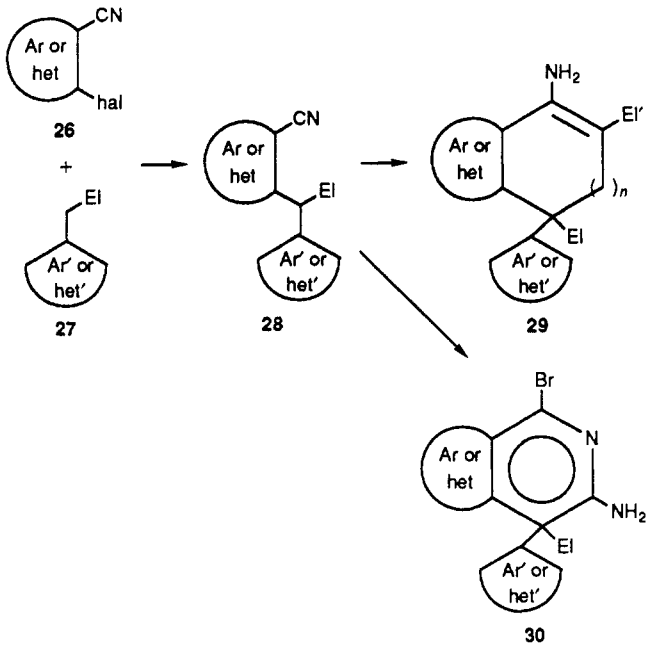
The examples given above indicate that the readily available (2-cyanoaryl)arylacetonitriles **28** give access to cyclopentene- and cyclohexene-annulated aromatics and heteroaromatics **29** as well as to [3,4]-condensed pyridines **16** and **30** (Scheme VI).

Experimental Section

General. All alkylation and cyclization reactions were performed under nitrogen. Potassium carbonate (Fluka) contained

(16) Filer, C. N.; Granchelli, F. E.; Soloway, A. H.; Neumeyer, J. L. *J. Org. Chem.* **1978**, *43*, 672.

Scheme VI[a]



[a] **a**, n = 0; **b**, n = 1.

less than 0.5% water (Karl Fisher titration). Potassium *tert*-butoxide was used as supplied (Fluka). Dimethylformamide was distilled from phosphorus pentoxide.[17] ^1H and ^{13}C NMR spectra were recorded on a Bruker AC-250 instrument; δ are in parts per million downfield from $SiMe_4$ as internal standard. Mass spectra were recorded on a V.G. Micromass 7070F instrument. Infrared spectra were obtained from solutions in CCl_4 with subtraction of solvent signals on a Perkin-Elmer 1720 Fourier transform spectrometer. Elemental analyses were performed by H. Lundbeck A/S, Copenhagen, Denmark.

Alkylation and Cyclization of (2-Cyanophenyl)phenylacetonitriles To Give 1-Amino-2-(methoxycarbonyl)-3-cyano-3-phenyl-1*H*-indenes (General Procedure). Methyl chloroacetate (6.0 g) was added with stirring to a mixture of (2-cyanophenyl)phenylacetonitrile (**3**, R = R′ = H) (10.0 g), potassium *tert*-butoxide (5.4 g), and dimethylformamide (50 mL). After being stirred for 3 h, the mixture was poured into a mixture of 0.1 M hydrochloric acid (200 mL), *n*-heptane (30 mL), and toluene (15 mL). Stirring for 1 h, filtration, and washing with water (2 × 50 mL), toluene (2 × 10 mL), and *n*-heptane (2 × 25 mL) afforded 12.2 g (92%) of 1-amino-2-(methoxycarbonyl)-3-cyano-3-phenyl-1*H*-indene (**5a**; R = R′ = H), mp 190–191 °C (ethanol). Anal. Calcd for $C_{18}H_{14}N_2O_2$: C, 74.45; H, 4.85; N, 9.65. Found: C, 74.4; H, 4.9; N, 9.25.

One-Pot Conversion of 2-Chlorobenzonitriles 1 into 1-Amino-2-(methoxycarbonyl)-3-cyano-3-phenyl-1*H*-indenes 5a (General Procedure). A mixture of 2-chlorobenzonitrile **1** (R = H) (12.3 g) and phenylacetonitrile **2** (R′ = H) (10 g) in dimethylformamide (25 mL) was added with stirring and cooling in an ice bath to potassium *tert*-butoxide (20.1 g) dissolved in dimethylformamide (50 mL) at such a rate that the temperature did not exceed 25 °C. After stirring for 0.5 h, methyl chloroacetate (11.1 g) was added in 10 min. After being stirred for 24 h, the mixture was worked up as above and the product recrystallized from ethanol. Yields of **5a** are given in Table I.

Cyclization of Methyl 3-Cyano-3-(*o*-cyanophenyl or heteroaryl)-3-phenylpropanoates (General Procedure). Methyl 3-cyano-3-(3-cyanothien-2-yl)-3-(4-fluorophenyl)propanoate (2.0 g) [prepared from (3-cyanothien-2-yl)(4-fluorophenyl)acetonitrile[1] and methyl chloroacetate as described below for the synthesis of **4c**], toluene (25 mL), and potassium *tert*-butoxide (0.2 g) were stirred for 1 h. Addition of saturated aqueous ammonium chloride (25 mL), drying of the organic solution (magnesium sulfate), and removal of the toluene gave 1.85 g (93%) of the crude product, which was recrystallized from diisopropyl ether. Yields are given in Table II.

Conversion of 1-Amino-2-(methoxycarbonyl)-3-cyano-3-aryl-1*H*-indenes 5a into 3-Aryl-1-oxoindan-3-carboxylic Acids 9a (General Procedure). 1-Amino-2-(methoxycarbonyl)-3-cyano-3-(4-fluorophenyl)-1*H*-indene (**5a**, R = H, R′ = 4-F) (50 g) and acetic acid (150 mL) were heated to 100°C; 60% aqueous sulfuric acid (100 mL) was added with stirring during 30 min. Stirring at 110 °C for 6 h, cooling, extraction with toluene (250 + 50 mL), washing with water (3 × 500 mL), extraction with 0.1 M aqueous sodium hydroxide (500 + 100 mL), acidification with concentrated hydrochloric acid, extraction with toluene (250 + 50 mL), filtration through activated carbon, and removal of the toluene gave 39.0 g (89%) of 3-(4-fluorophenyl)-1-oxoindan-3-carboxylic acid (**9a**, R = H, R′ = 4-F), which crystallized on standing, mp 106–108 °C (diisopropyl ether). Anal. Calcd for $C_{16}H_{11}O_3F$: C, 71.0; H, 4.2. Found: C, 71.0; H, 4.2.

Decarboxylation of 3-Aryl-1-oxoindan-3-carboxylic Acids 9a (General Procedure). 3-(4-Fluorophenyl)-1-oxoindan-3-carboxylic acid (**9a**, R = H, R′ = 4-F) (25 g) and *N*-methylpyrrolidone (50 mL) were heated slowly to 100 °C and kept at this temperature for 1 h. After cooling, the solution was poured into water (200 mL) with efficient stirring. Filtration, washing with water (3 × 100 mL), dissolution in ethyl acetate (200 mL), filtration through activated carbon, and removal of the ethyl acetate gave 18.4 g (88%) of 3-(4-fluorophenyl)indan-1-one (**10a**, R = H, R′ = 4-F), mp 121–123 °C (ethanol). Anal. Calcd for $C_{15}H_{11}OF$: C, 79.6; H, 4.9. Found: C, 79.5; H, 4.85. δ_H ($CDCl_3$): 7.90–7.75 (1 H, m, H-7), 7.71–6.85 (7 H, m, H-4–H-6 + Ph), 4.57, 3.18 and 2.70 (3 H, ABX pattern, J = 19.0 Hz, H-3, H-2b, and H-2a).

Alkylation and Cyclization of (2-Cyanophenyl)phenylacetonitriles 3 Generated in Situ into 1-Amino-2,3-dicyano-3-phenyl-1*H*-indenes 5a (El′ = CN). As described for the preparation of **5a** from **1**, 2-chlorobenzonitrile (5.4 g), (4-fluorophenyl)acetonitrile (5.4 g), and chloroacetonitrile (3.5 g) afforded 9.0 g (90%) of 1-amino-2,3-dicyano-3-(4-fluorophenyl)-1*H*-indene (**5a**, R = H, R′ = 4-F, El′ = CN), mp 175–177 °C. Anal. Calcd for $C_{17}H_{10}N_3F$: C, 74.15; H, 3.65; N, 15.25. Found: C, 74.4; H, 3.6; N, 15.05.

Methyl 4-Cyano-4-(2-cyanophenyl)-4-(4-fluorophenyl)butanoate (4b). (2-Cyanophenyl)(4-fluorophenyl)acetonitrile (**3**, R = H, R′ = 4-F) (20 g) was added with efficient stirring to a mixture of potassium carbonate (14 g), tetrabutylammonium hydrogen sulfate (2.9 g), and dimethylformamide (100 mL). After stirring for 15 min, methyl acrylate (8.8 g) was added with cooling, maintaining the temperature at ca. 20 °C. Stirring for 3 h, addition of saturated aqueous ammonium chloride (300 mL), extraction with ethyl acetate (100 mL), and removal of the ethyl acetate gave 25 g (91%) of **4b** (R = H, R′ = 4-F), mp 97–100 °C (diisopropyl ether). Anal. Calcd for $C_{19}H_{13}N_2O_2F$: C, 70.8; H, 4.7; N, 8.7. Found: C, 71.2; H, 4.8; N, 8.5.

Cyclization of methyl 4-cyano-(2-cyanophenyl)-4-(4-fluorophenyl)butanoate (4b, R = H, R′ = 4-F) was performed as described above in the cyclization of methyl 3-cyano-3-(*o*-cyanophenyl)-3-phenylpropanoates, producing 85% of 1-amino-2-(methoxycarbonyl)-4-cyano-4-(4-fluorophenyl)-3,4-dihydronaphthalene (**5b**, R = H, R′ = 4-F), mp 167–169 °C (ethanol). Anal. Calcd for $C_{19}H_{15}N_2O_2F$: C, 70.8; H, 4.7; N, 8.7. Found: C, 70.45; H, 4.85; N, 8.4. δ_H ($CDCl_3$): 7.73–6.85 (8 H, m, H-5–H-8 + Ph), 6.59 (2 H, br s, NH_2), 3.71 (3 H, s, OMe), 3.40 and 3.21 (2 H, AB pattern, J = 15.4 Hz, CH_2).

Conversion of 1-Amino-2-(methoxycarbonyl)-4-cyano-4-aryl-3,4-dihydronaphthalenes 5b into 4-Aryl-3,4-dihydro-1-oxo-1(2*H*)-naphthalene-4-carboxylic Acids 9b. 1-Amino-2-(methoxycarbonyl)-4-cyano-4-(4-fluorophenyl)-3,4-dihydronaphthalene (**5b**, R = H, R′ = 4-F) (24.5 g) and acetic acid (125 mL) were heated to 100 °C; 67% aqueous sulfuric acid (60 mL) was added with stirring during 15 min. Stirring at 115 °C for 18 h, cooling, extraction with toluene (200 mL), washing with water (3 × 500 mL), extraction with 1 M aqueous sodium hydrogen carbonate (200 mL), acidification with 4 M hydrochloric acid, extraction with toluene, filtration through activated carbon, and removal of the toluene gave 14.7 g (68%) of 4-(4-fluorophenyl)-3,4-dihydro-1-oxo-1(2*H*)-naphthalene-4-carboxylic acid

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(**9b**, R = H, R′ = 4-F) as an oil, which crystallized on standing, mp 147–149 °C (diisopropyl ether). Anal. Calcd for $C_{17}H_{13}O_3F$: C, 71.8; H, 4.6. Found: C, 72.1; H, 4.75.

Decarboxylation of 4-Aryl-3,4-dihydro-1-oxo-1(2*H*)-naphthalene-4-carboxylic acids 9b into 4-aryl-3,4-dihydro-1(2*H*)-naphthalen-1-ones 10b was performed as described for the conversion of **9a** to **10a** and heating to 100 °C for 15 h. In this way, 4-(4-fluorophenyl)-3,4-dihydro-1-oxo-1(2*H*)-naphthalene-4-carboxylic acid (**9b**, R = H, R′ = 4-F) produced 85% of 4-(4-fluorophenyl)-3,4-dihydro-1(2*H*)-naphthalen-1-one (**10b**, R = H, R′ = 4-F), mp 68–70 °C. Anal. Calcd for $C_{16}H_{16}OF$: C, 79.8; H, 5.45. Found: C, 79.9; H, 5.45. δ_H ($CDCl_3$): 8.20–8.09 (1 H, m, H-8), 7.50–6.88 (7 H, m, H-5–H-7 + Ph), 4.35 (1 H, dd, H-4), 2.84–2.13 (4 H, m, $2CH_2$).

Methyl 5-Cyano-5-(2-cyanophenyl)-5-phenylpentanoate (4c). A solution of phenylacetonitrile (10.0 g) and 2-chlorobenzonitrile (12.3 g) in dimethylformamide (25 mL) was added with stirring to a solution of potassium *tert*-butoxide (20.1 g) in dimethylformamide (80 mL). After stirring for 1 h, methyl 4-bromobutyrate (20.0 g) was added at such a rate that the temperature did not exceed 30 °C. Stirring overnight, addition of saturated aqueous ammonium chloride (200 mL), extraction with ethyl acetate (2 × 100 mL), and removal of the ethyl acetate gave 25.4 g of crude product. Recrystallization (diisopropyl ether) gave 21.2 g (78%) of **4c** (R = R′ = H), mp 75–77 °C. Anal. Calcd for $C_{20}H_{18}N_2O_2$: C, 75.45; H, 5.7; N, 8.8. Found: C, 75.45; H, 5.7; N, 8.85.

Cyclization of methyl 5-cyano-5-(2-cyanophenyl)-5-phenylpentanoate (4c, R = R′ = H) was performed as described above in the cyclization of methyl 3-cyano-3-(*o*-cyanophenyl)-3-phenylpropanoates, replacing toluene with chlorobenzene, producing 81% of 5-amino-3-(methoxycarbonyl)-9b-phenyl-2,9b-dihydro-1*H*-cyclopent[*c*]isoquinoline (**15**, R = R′ = H), mp 205–206 °C (methanol). Anal. Calcd for $C_{20}H_{18}N_2O_2$: C, 75.45; H, 5.7; N, 8.8. Found: C, 75.35; H, 5.7; N, 8.85. IR (cm^{-1}): 3345 (NH), 1710 (COOR), 1685 (C=N). MS: *m/e* 318 (100, M^+). δ_H ($CDCl_3$): 7.74 (1 H, br s, H-6), 7.57 (1 H, dt, H-8), 7.55 (1 H, dd, H-9), 7.37 (1 H, dt, H-7), 7.22–7.12 (5 H, m, Ph), 3.80 (3 H, s, OMe), 2.70–2.44 (4 H, m, $2CH_2$). δ_C ($CDCl_3$): 166.6 (C=O), 156.8 (C-5), 155.7 (C-3a), 143.0 (C-1′), 131.6 (C-8), 128.4 (C-6), 128.4 (C-3′), 127.0 (C-7), 126.8 (C-4′), 126.2 (C-9), 125.9 (C-2′), 125.4 (C-5a), 105.6 br (C-3), 55.7 (C-9b), 51.1 (CH_3O), 37.7 (C-2), 27.6 (C-1). C-9a (145.3) is only observed in d_6-DMSO solution. The assignments were supported by H,H-, C,H-, and C,C,H-correlated (COLOC) 2D NMR spectra.

3-(Methoxycarbonyl)-9b-phenyl-2,9b-dihydro-1*H*-cyclopent[*c*]isoquinolin-5-one (16). Compound **15** (0.86 g), pyridine (4.1 mL), and acetyl chloride (0.57 mL) were mixed at 0 °C and stirred at 20 °C for 3 h. Evaporation to dryness gave a monoacetyl derivative (δ_H ($CDCl_3$): CH_3CO at 2.45 ppm) contaminated with pyridinium hydrochloride. This residue dissolved in dichloromethane (20 mL) was stirred with 1 M hydrochloric acid (20 mL) for 2 days. The organic solution was isolated, washed with saturated sodium hydrogen carbonate, dried, and evaporated to dryness, leaving 3-(methoxycarbonyl)-9b-phenyl-2,9b-dihydro-1*H*-cyclopent[*c*]isoquinolin-5-one (**16**) in quantitative yield as a yellow oil. Anal. Calcd for $C_{20}H_{17}NO_3$: C, 75.2; H, 5.35; N, 4.4. Found: C, 75.0; H, 5.6; N, 4.2. IR (cm^{-1}): 1660. MS: *m/e* (68, M^+). δ_H ($CDCl_3$) 8.11 dd (1 H, dd, J = 1.4 and 8.2 Hz, H-6), 7.64 (1 H, dt, H-8), 7.51 (1 H, dd, H-9), 7.41 (1 H, dt, H-7), 7.26–7.14 (5 H, m, Ph), 3.82 (3 H, s, OMe), 3.47 (1 H, s, exchangeable, NH), 2.74–2.49 (4 H, m, 2 × CH_2). δ_C ($CDCl_3$): 166.0 (COOR), 162.8 (CONH), 153.2 (C-3a), 144.1 (C-9a), 142.6 (C-1′), 133.2 (C-8), 128.6 (C-6), 128.5 (C-3′), 127.3 (C-7), 127.0 (C-4′), 125.9 (C-5a), 125.7 (C-9), 125.6 (C-2′), 107.1 (C-3), 55.5 (C-9b), 51.3 (CH_3O), 37.5 (C-2), 27.4 (C-1). The assignments were based on H,H-, C,H-, and C,C,H-correlated (COLOC) 2D NMR spectra.

5-Amino-4-cyano-2,3-dihydro-1*H*-benz[*e*]indene (19). A solution of (cyclopenten-1-yl)acetonitrile (5.0 g) and 2-chlorobenzonitrile (6.7 g) in dimethylformamide (20 mL) was added with cooling in an ice bath to a solution of potassium *tert*-butoxide (5.5 g) in dimethylformamide (20 mL) at such a rate that the temperature did not exceed 25 °C. Stirring at 20 °C for 0.5 h, addition of saturated aqueous ammonium chloride (55 mL), extraction with ethyl acetate (2 × 30 mL), removal of the ethyl acetate, and recrystallization (methanol) gave 7.3 g (75%) of **19**, mp 185–186 °C. Anal. Calcd for $C_{14}H_{12}N_2$: C, 80.75; H, 5.8; N, 13.45. Found: C, 80.65; H, 5.65; N, 13.5. δ_H ($CDCl_3$): 8.07 (1 H, d, H-8), 7.75 (1 H, d, H-5), 7.55 (1 H, t, H-7), 7.43 (1 H, t, H-6), 4.57 (2 H, br s, NH_2), 3.25 (2 H, t, CH_2-C-4), 2.87 (2 H, t, CH_2-C-3), 2.21 (quintet, CH_2). A nuclear Overhauser effect is observed between the signals at 3.25 and 7.75 ppm and between the signals at 7.75 and 7.43 ppm.

Acid-Catalyzed Cyclization of *o*-Cyanoaryl or Heteroaryl Acetonitriles (General Procedure). 2-(Cyanophenyl)(4-fluorophenyl)acetonitrile (**3**, R = H, R′ = 4-F) (10 g) and 30% HBr in acetic acid (50 mL) were stirred for 2 h. Addition of ether (50 mL), filtration, washing with ether (2 × 25 mL), suspension in ethyl acetate (200 mL), neutralization with saturated aqueous sodium hydrogen carbonate, isolation of the organic phase, removal of the ethyl acetate, and recrystallization from ethanol gave 11.2 g (84%) of 1-bromo-3-amino-4-(4-fluorophenyl)isoquinoline (**7**, R = H, R′ = 4-F), mp 200–202 °C. Anal. Calcd for $C_{15}H_{10}N_2BrF$: C, 56.8; H, 3.2; N, 8.85. Found: C, 56.45; H, 3.1; N, 8.5.

Similarly, (3-cyanothien-2-yl)(4-fluorophenyl)acetonitrile (**20**)[1] gave 83% of 4-bromo-7-(4-fluorophenyl)thieno[3,2-*c*]pyridine (**24**), mp 185–187 °C (ethanol). Anal. Calcd for $C_{13}H_8N_2SBrF$: C, 48.3; H, 2.5; N, 8.65. Found: C, 48.0; H, 2.55; N, 8.4.

Similarly, (3-cyanopyrid-2-yl)(4-fluorophenyl)acetonitrile (**22**)[1] gave 82% of 5-bromo-8-(4-fluorophenyl)-1,6-naphthyridine (**25**), mp 238–240 °C (ethanol). Anal. Calcd for $C_{14}H_9N_3BrF$: C, 52.85; H, 2.85; N, 13.2. Found: C, 52.5; H, 2.9; N, 12.9.

Debromination of 1-bromo-3-amino-4-(4-fluorophenyl)-isoquinoline (7, R = H, R′ = 4-F) was performed by using the procedure described in ref 18 and afforded 70% of 3-amino-4-(4-fluorophenyl)isoquinoline (**8**, R = H, R′ = 4-F), mp 150–152 °C (ethanol). Anal. Calcd for $C_{15}H_{11}N_2OF$: C, 75.6; H, 4.65; N, 11.75. Found: C, 75.5; H, 4.65; N, 11.75.

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