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LETTERS

A Short Route to Multiply Substituted Fluorenones

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Abstract:
We report a two-step synthesis of polysubstituted fluorenones by condensation of malononitrile with aromatic aldehydes and methylketones or with β-aryl-α,β-unsaturated carbonyl compounds, aldehydes or ketones. The yields of the fluorenone systems depend on the nature of the substitution on the aromatic rings.

As a part of our research on new materials,[1] we attempted to develop a general approach to the synthesis of multiple substituted fluorenones to be used as a central core in calamitic mesogens. We are especially interested in those with asymmetrical substitution, which may generate the high dipole moment required to induce a liquid crystalline order. Although different methods have been reported for the preparation of substituted fluorenones: 1) introduction and transformation of functional groups in the fluorenone system,[2] 2) intramolecular cyclization of diaryl ketones,[3] or 3) intramolecular cyclization of biphenyl compounds,[4] they are usually applied to simple systems, such as monosubstituted or disubstituted fluorenones.

To our knowledge, very little attention has been paid to highly substituted fluorenones, especially asymmetrical ones. The reason may be the difficulty of their preparation. We have successfully utilized an intramolecular cyclization approach to the synthesis of multiply substituted fluorenones (Figure 1) by a general route through alkylsubstituted 3-aminobiphenyl-2,4-dicarbonitriles. These polysubstituted biphenyl compounds can be prepared from simple starting materials in a one-pot reaction, by condensation of activated nitriles with aromatic aldehydes and methylketones or alternatively with β-aryl-α,β-unsaturated ketones or aldehydes.

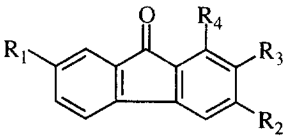

Fig. 1. asymmetrical multiply substituted fluorenones

RESULTS AND DISCUSSION

The general method followed is outlined in Scheme 1. It was reported[5] that α,β-unsaturated ketones react with malononitrile when potassium fluoride is used as catalyst through a Knoevenagel reaction, followed by conjugate addition and intramolecular condensation to yield 2-aminocyclohexadiene-1,1,3-tricarbonitriles. The cyclohexadiene derivatives are prone to aromatization by elimination of hydrogen cyanide[6] giving 2-

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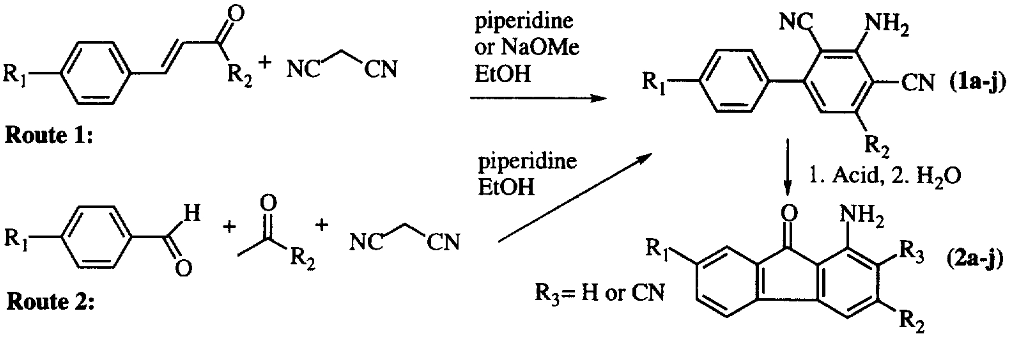
aminobenzene-1,3-dicarbonitriles.[7,8] Thus the desired alkylsubstituted 3-aminobiphenyl-2,4-dicarbonitriles can be prepared from malononitrile and the corresponding β-aryl-α,β-unsaturated ketones or aldehydes in the presence of piperidine. The data on the dicarbonitriles obtained is given in Table 1. As starting materials we used either β-aryl-α,β-unsaturated carbonyls, ketones or aldehydes (Scheme 1, Route 1), or equimolar mixtures of aromatic aldehydes and alkylketones (Scheme 1, Route 2).



Scheme 1. Synthetic scheme of the preparation of polysubstituted biphenyl and fluorenone systems

Table 1: Preparation of Biphenyl Compounds (**1**).

Product (**1**)	R_1	R_2	Yields (%)
a	H	H	8
b	H	Me	35
c	Me	Me	32
d	Me	i-Pr	10
e	i-Pr	Me	28
f	Br	Me	44
g	Cl	Me	42
h	MeO	Me	38
i	CHO	Me	41
j	H	Ph	15

With these dicarbonitriles in hand, we started to study their intramolecular cyclizations. Friedel-Crafts acylation with nitriles as acylating agents was studied in the early part of this century by Hoesch,[9] and later by Houben[9], who demonstrated that the acylation of phenols and phenol ethers could be achieved in good yields by reaction with nitriles and dry HCl, usually in the presence of a Lewis acid, such as $ZnCl_2$ or $AlCl_3$. However, the first attempts of intramolecular cyclization of the 3-aminobiphenyl-2,4-dicarbonitriles were unsuccessful using the general procedure of Houben-Hoesch Reaction (HCl and zinc chloride, nitromethane as solvent; Table 2, entry 1) and also by treatment with pure hydrofluoric acid at room temperature or at 30°Cfor 14 hours (Table 2, entry 2 and 3).

Table 2: Cyclizations Conditions Assayed to Prepare Fluorenone Systems.

Entry	Reagents	Temp. (C)	time (h)	Yield (%)[1]	Product
1	$HCl/ZnCl_2$	0°C 8h; rt 48 h	56	0	-[2]
2	HF	rt (< 20)	16	0	-[2]
3	HF	30	14	0	-[2]
4	CF_3SO_3H	rt	24	22	R_3=CN
5	100% H_3PO_4	95-100	24	33	R_3=H

Note: [1]All the yields are referred for compound (**1h**). [2] The starting material was recovered.

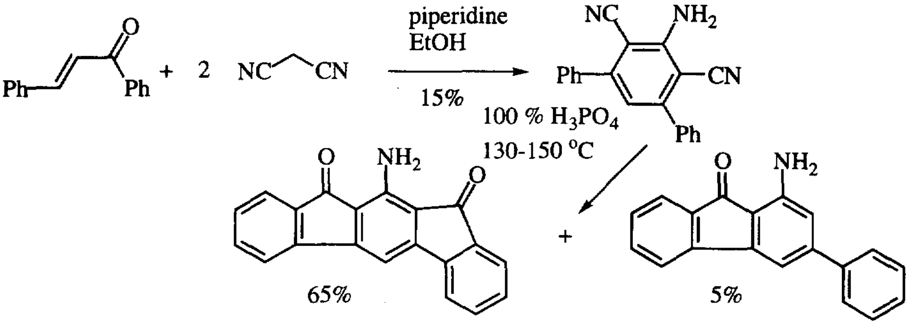
Different attempts at cyclization were assayed with the dicarbononitrile (**1h**) and are collected in Table 2. The use of trifluoromethanesulfonic acid, (Table 2, entry 4) yielded the cyclization product without loss of the second cyano group. However, when the 3-aminobiphenyl-2,4-dicarbonitriles were treated with polyphosphoric acid at 100°C, the cyclization products obtained were those, in which decyanation of the second cyano group was observed simultaneously (R_3=H, Scheme 1). In this way, polysubstituted fluorenones were prepared with moderate to good yields (Table 3). Compounds (**2**) can be easily converted into a large variety of derivatives through diazonium salts. As a result of our experiments, the synthesized dicarbonitriles are excellent precursors of fluorenone systems.

Table 3: Preparation of Substituted Fluorenones (**2**).

Product (**2**)	R_1	R_2	Yield (%)
a	H	H	55
b	H	Me	68
c	Me	Me	65
d	Me	*i*-Pr	62
e	*i*-Pr	Me	64
f	Br	Me	16
g	Cl	Me	12
h	MeO	Me	33
i	CHO	Me	0

Note: [1]In all the cases R_3 = H.

It is worth mentioning the behaviour of 2-amino-4,6-diphenylbenzene-1,3-dicarbonitrile. When this compound was treated under cyclization conditions, polyphosphoric acid at 130-150°C, the dicyclization product, 11-amino-indeno(2,1-b)fluorene-10,12-dione, was found to be the major product (65%), while only a small amount (5%) of the decyanation product was detected (scheme 2).



Scheme 2. Double cyclization of 2-amino-4,6-diphenylbenzene-1,3-dicarbonitrile

The nature of the substitution pattern in the biphenyl compound affects the yield of the cyclization reaction, as in all Friedel-Craft acylations. When the substituents were halogens (Br, Cl) or carbaldehyde, the yields were lower and little or no product was detected. In the case of a methoxy substituent, the yield obtained was only 33 %, because some product was lost as the phenyl derivative by cleavage of the ether function under the strong acid conditions used in the cyclization reaction (Table 3).

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