Tetrahedron Letters, Vol.31, No.19, pp 2735-2738, 1990
Printed in Great Britain

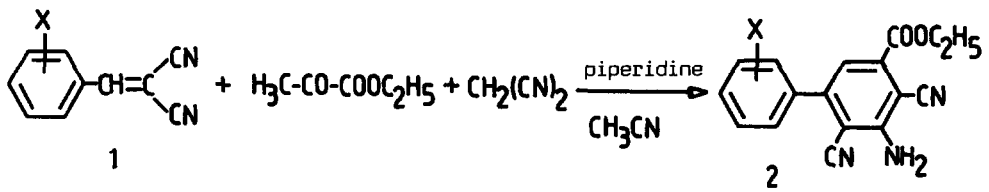
0040-4039/90 $3.00 + .00
Pergamon Press plc

NEW SYNTHESIS OF SUBSTITUTED BIPHENYLS, BIARYLS, AND TERPHENYLS FROM ARYLIDENEMALONODINITRILES, ETHYL PYRUVATE, AND MALONODINITRILE

Piotr Milart and Janusz Sepioł
Department of Organic Chemistry, Jagiellonian University
30-060 Krakow, Karasia 3, Poland

Abstract: The reaction of arylidenemalonodinitriles with ethyl pyruvate and malonodinitrile affords in one step ethyl 3-amino-2,4-dicyano-5-aryl-benzoates (**2**) which are then used in synthesis of 3-amino-5-arylbenzoic acids (**4**).

We wish to report on a new and efficient synthesis of the benzene system bearing an aryl substituent, two nitrile functions, the amino, and the ester group. These penta-substituted benzenes **2** are prepared in a one-pot synthesis in acetonitrile solution from easily available arylidenemalonodinitriles **1**, ethyl pyruvate, and malonodinitrile. The dicyanovinyl moiety of arylidenemalonodinitriles is the essential part of these compounds on which a new benzene system is constructed.

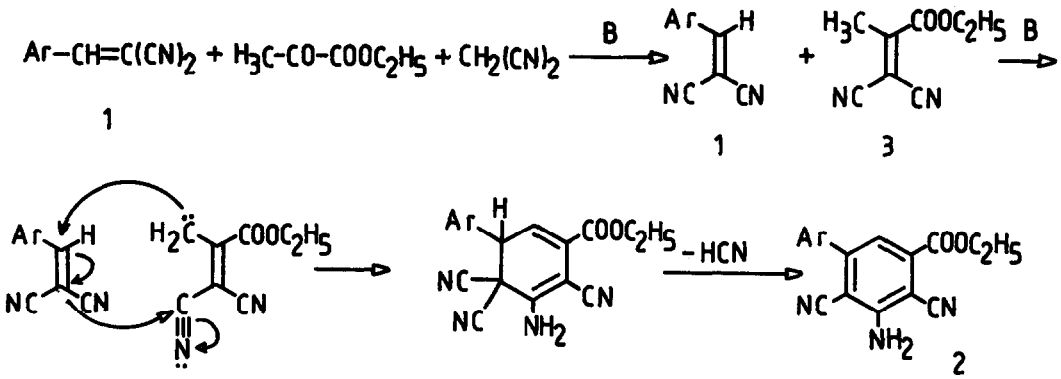


1 2

a) X = H; b) X = o-CH_3; c) X = m-CH_3; d) X = p-CH_3; e) X = p-OCH_3; f) X = m-NO_2; g) X = p-NO_2; h) X = p-CN

The condensation product of ethyl pyruvate and malonodinitrile - ethyl 2-dicyanomethylenepropanoate (**3**) (EDMP) - attracted our attention as a potentially useful compound for the synthesis of aromatic systems (Scheme 1). The preparation of EDMP has been reported a long time ago but received little application in organic synthesis [1]. The presence of three strongly electron attracting substituents in the molecule of EDMP - two nitrile groups and the ester function - may enchance the ease of formation of an anion on the lone methyl group of **3** under the influence of relatively weak bases. The anion is considerably stabilized by the delocalization of the negative charge over the whole molecule of **3**.

Scheme 1

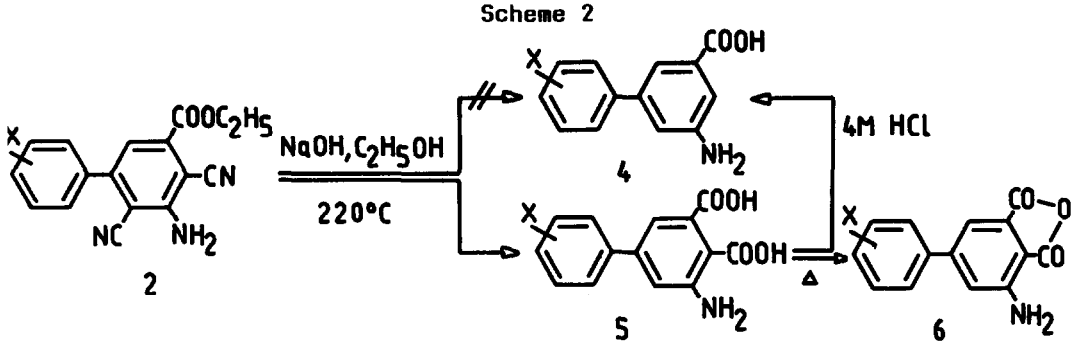


We have assumed that, in the presence of bases, EDMP may undergo the Michael addition to the dicyanovinyl moiety of arylidenemalonodinitriles. The Thorpe cyclization of the adduct followed by the elimination of hydrogen cyanide could lead to the formation of substituted benzene **2**. However, the notorious tendency of **3** to dimerize [2] and therefore its instability for a prolonged time forced us to modify further our approach. We have decided to synthesize **3** in situ in the presence of arylidenemalonodinitriles. Thus, the above described modification allowed us to avoid tedious preparation of EDMP (**3**) and reduced the synthesis of substituted biaryls **2** to a single synthetic step (Scheme 1).

General procedure for the preparation of substituted biaryls **2**: Arylidenemalonodinitriles **1** (0.01 mol), ethyl pyruvate (0.01 mol), and malonodinitrile (0.011 mol) are dissolved in acetonitrile (20 ml) and several drops of piperidine are added under magnetic stirring. The solution darkens and warms up. After being stirred at room temp. for a few minutes the solution is then refluxed and stirred for 1.5 h. Some less soluble biaryls **2** separate during heating under reflux. The solution is left overnight in a refrigerator and separated biaryls **2** are usually recrystallized from nitromethane or a mixture nitromethane-ethanol [3].

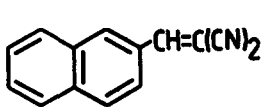
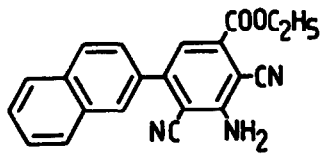
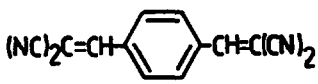
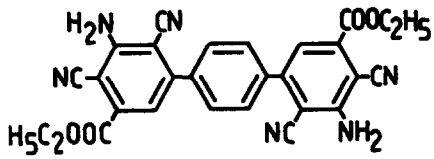
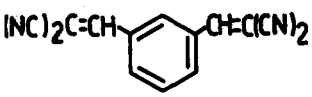
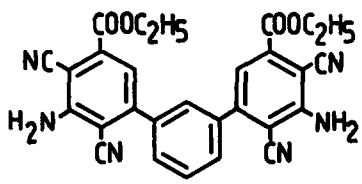
Substituted biphenyls **2** and biaryls are potentially useful starting compounds in a variety of syntheses. All functional groups of **2** may be selectively transformed or removed. Thus, in connection with our earlier investigations [4] we hoped that heating **2** in ethanolic solution of sodium hydroxide in an autoclave at 200-220°C may cause the hydrolysis and decarboxylation of both nitrile groups in the ortho positions with respect to the amino function. However, to our surprise, after heating some biaryls **2** for several hours in an autoclave at the above mentioned conditions, we isolated sodium salts of dicarboxylic acids **5** instead of expected 3-amino-5-arylbenzoic acids **4**. (Scheme 2) Free 3-amino-5-aryl-1,2-benzenedicarbox-

Scheme 2



i) X = m-NH_2; j) X = p-NH_2; k) X = p-COOH

Table 1. Synthesis of Biaryls and Terphenyls from Arylidenemalononitriles

Arylidenemalononitrile	Product	M.p.	Yield (%)
		255-6°C	43
		342-3°C	19
		310-1°C	26

ylic acids **5** are easily obtained from these salts. Aparently, the carboxylic group of **5** having the amino and the carboxylic functions in both ortho positions does not decarboxylate in strongly basic solutions even under severe reaction conditions involving heating in an autoclave at high temperature [5]. On the other hand, acids **5** loose water very easily when heated or sublimed under reduced pressure and form anhydrides **6** [6]. Our target 3-amino-5-arylbenzoic acids **4** were eventually obtained from **5** on refluxing in 4M hydrochloric acid [7]. At these conditions the carboxylic group of **5** in the ortho position with respect to the amino function is efficiently removed. In contrast to other amino-biphenylcarboxylic acids

with a variety of substitution pattern, 3-amino-5-aryl-benzenecarboxylic acids **4** belong to a group of compounds which were not previously synthesized and investigated.

Acknowledgment: Financial support of this research by the Polish Academy of Sciences (CPBP 01.13) is gratefully acknowledged.

References and Notes

1. Hori, T.; Nakanishi, K., Chem. Commun. **1969**, 528; Yamada, Y.; Iguchi, K.; Hosaka, K.; Hagiwara, K., Synthesis **1974**, 669.
2. Cornelis, A.; Failon, A.; Laszlo, P., Bull. Soc. Chim. Belg. **1976**, 85, 141.
3. M.ps and yields of biphenyls **2**: **2a**: 212-3°C (40%), **2b**: 163-4°C (21%), **2c**: 215°C (32%), **2d**: 239-40°C (36%), **2e**: 193-4°C (34%), **2f**: 277-8°C (30%), **2g**: 287-8°C (30%), **2h**: 278-9°C (34%). Compounds **2i** and **2j** (Scheme 2) were obtained by the reduction of nitro-biphenyls **2f** and **2g**, respectively, with stannous chloride in absolute ethanol following the reported method (Grunewald, G. L.; Paradkar, V. M.; Pazhenchevsky, B.; Pleiss, M. A.; Sall, D. J.; Seibel, W. L., Reitz, T. J., J. Org. Chem. **1983**, 48, 2321; Bellamy, F. D.; Ou, K., Tetrahedron Lett. **1984**, 25, 839), **2i**: 245-6°C (49%), **2j**: 271-2°C (66%). The presence of electron-withdrawing or electron-releasing substituents in the aromatic ring of arylidenemalonodinitriles seems to have little effect on the course of reaction leading to biaryls and biphenyls **2**. However, steric effects of substituents in the ortho position of arylidenemalonodinitriles are of substantial importance. Thus, o-nitrobenzylidenemalonodinitrile and 1-naphthylidenemalonodinitrile failed to give expected products, presumably due to the steric hindrance involved in the formation of the Michae adducts (Scheme 1). On the other hand, 2-naphthylidenemalonodinitrile afforded substituted biaryl in 43% yield (Table 1.). All new compounds **2**, **4**, **5**, and **6** exhibited spectroscopic data (MS, IR, NMR) in accord with the assigned structures and gave satisfactory combustion analyses.
4. Sepioł, J., Synthesis **1983**, 504, 559.
5. Typical experimental procedure for synthesis of substituted biphenyls **5**: Biphenyl **2** (4 mmol) and sodium hydroxide (3.0 g) are dissolved in ethanol (60 ml) and heated for 3-4 h at 220°C in a 250 ml autoclave. A slurry of sodium salts of dicarboxylic acids **5** is obtained. Ethanol is removed and the salt is dissolved in a small amount of water. The solution is neutralized with hydrochloric acid until the precipitation of **5** is complete.
6. **6a**: m.p. 172-3°C, **6c**: m.p. 211-2°C, **6d**: m.p. 209-10°C.
7. Dicarboxylic acid **5** (1 mmol) is suspended in 4M hydrochloric acid (10 ml) and magnetically stirred and heated under reflux for 2 h. The precipitate is dissolved in a dilute solution (5%) of sodium hydroxide and then neutralized with acetic acid until separation of **4** is complete. m-Aminocarboxylic acids **4** are conveniently purified by sublimation under reduced pressure; **4a**: 218-9°C (48%), **4c**: 189-90° (76%), **4d**: 227-8°C (48%), **4j**: 247°C (51%), **4k**: 303-4°C (45%).

(Received in UK 28 February 1990)