Aromatic Benzene Compounds from Acyclic Precursors

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1 Introduction

The synthesis of substituted aromatic hydrocarbons has been a feature of synthetic organic chemistry from almost its beginnings early in the nineteenth century and owes much to the pioneering work of A. W. Hofmann from 1845 onwards. At that time coal tar provided a cheap and plentiful supply of benzene as well as several other aromatic hydrocarbons and so the early synthetic routes to substituted benzenes almost inevitably started from these cheap feedstocks. The required substitution patterns were then achieved by subjecting the appropriate hydrocarbon to a series of stepwise reactions, *e.g.* nitration, sulphonation, chlorination, reduction, oxidation. Consequently, a vast body of literature is now available concerned with both nucleophilic and electrophilic substitutions at the benzene ring and some very elegant and effective syntheses of substituted benzenes are to be found. Hence, today, ring functionalization is the most important method for preparing substituted benzenoids.

Ring functionalization is not the only synthetic strategy that can be envisaged since it is also possible to construct the ring with some or all of the substituents already in place starting from acyclic precursors. This strategy can best be seen in the field of heterocyclic synthesis where many heterocycles, *e.g.* pyrroles, pyridines, and pyrimidines, are often best prepared from acyclic precursors.*

It is not surprising therefore to find that benzene compounds can also be prepared by the same strategy and this is most emphatically confirmed in biochemical synthesis where nature is a most elegant practiser of the ring synthesis method, *e.g.* the synthesis of anthranilic acid. Several advantages can be seen in this approach such as the preparation of highly substituted compounds in only a few steps and the avoidance of *ortho–meta–para* mixtures common in conventional aromatic synthesis. Generally, highly substituted benzenes require long synthetic routes by conventional methods and this tends to negate the advantages of using cheap and readily available starting materials. Ring synthesis can also provide substitution patterns not easily attained by conventional synthesis and therefore new compounds previously untested, in for example pharmaceutical and plant protection products, could be made available. In addition, the introduction of labels (^{13}C, ^{14}C) into aromatic compounds, not an easy task by conventional synthesis, should be easier by ring synthesis in view of the greater availability of labelled acyclic compounds.

* In this review heterocycles will therefore be considered as masked acyclic compounds.

2 Scope and Organization

The scope of this review has been limited so as to keep its length within reasonable bounds. Therefore, only syntheses of benzene rings are considered; however, several examples of condensed-ring systems are presented but only where the additional rings are non-aromatic. Reactions involving cycloadditions, the most important of which is the Diels–Alder reaction, have been omitted since many reviews already cover this area.[1] The vast majority of the syntheses considered here, therefore, involve condensation reactions (Aldol, Claisen *etc.*) and addition reactions, *e.g.* the Michael addition. In some sections a few aromatization reactions have been highlighted, although this topic in itself is a subject worthy of a major review.

The review has been organized into four sections (Sections 3—6) depending upon the nature of the substituents in the benzene ring. The first section (3A—C) contains all those benzenes with at least one hydroxy-group and necessarily contains hydroxybenzenes with other groups, *e.g.* cyano, ester *etc.* The second section (4) contains all those benzenes with an amino-group, but not an amino- and a hydroxy-group since these are to be found in section one. The third and fourth sections (5 and 6) describe benzenes containing electron acceptors and alkyl groups only, respectively. Hence the synthesis of a benzene containing cyano-, hydroxy-, and amino-groups will be found in the first section. This classification is rather arbitrary but classing the syntheses by functionality probably presents the material in a much more useful format for the chemist who is looking for an alternative to a ring functionalization approach. The use of the alternative fragment approach, *e.g.* 4 + 2, 3 + 3 *etc.*, or an approach which considers reactive centres in the acyclic precursors have therefore been omitted as being of less use in meeting the desired aims of this review.

3 Hydroxybenzenes

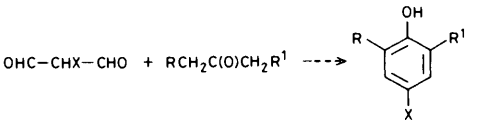
This section contains the largest number of references and has been further split into three categories; phenols, dihydroxybenzenes (catechols, resorcinols, hydroquinones), and benzenes containing more than two hydroxy-groups.

A. Phenols.—In the ring synthesis method the phenolic hydroxy-group usually comes from the carbonyl oxygen of either a ketone or an ester group and with the abundance of different ketones and esters a wide range of phenols can be synthesized, as the following text illustrates. Ketones usually react as three-carbon components *via* the two active and nucleophilic α-positions. The co-reactant therefore must also be a three-carbon component but with two sites of complementary activity, *i.e.* electrophilic. The most common co-reactant is a β-dicarbonyl compound, or synthetic equivalent thereof, and a large number of reactions of this type have been reported.

[1] (*a*) H. Wollweber, 'Diels–Alder Reaktion', G. T. Verlag, Stuttgart, 1972; (*b*) S. Danishefsky, *Acc. Chem. Res.*, 1981, **14**, 400; (*c*) G. Brieger and J. N. Bennett, *Chem. Rev.*, 1980, **80**, 63, and references cited therein.

Malondialdehydes are the simplest β-dicarbonyl compounds and have been studied for nearly a century. They react with various ketones to give the corresponding phenols in fair to good yields as shown in Table 1. In particular the condensation of malondialdehydes carrying electron-withdrawing substituents has received close attention from a number of workers. Thus, Hill and co-workers did much of the pioneering work on 2-nitromalondialdehydes around 1900. Unfortunately, the synthetic utility of this approach is severely limited by the chemical instability and expense of many malondialdehydes and the preparation of

Table 1 *Condensation of malondialdehydes*

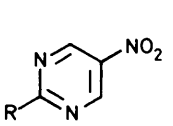


Entry	X	R	R^1	*Yield* (%)	*Ref.*	*Comments*
1	H	CO_2R	CO_2R	41	2	
2	NO_2	H	H	64	3*a*—*d*	3*d* ^{14}C labelled acetone used
3	NO_2	H	Et	70	4	
4	NO_2	H	CH_2CO_2H	82	3*c*	
5	NO_2	H	Ph	88	5*ab*	
6	NO_2	H	OPh	78	6	
7	NO_2	Me	Me	94	4	
8	NO_2	Ph	Ph	95	5*a*,4	
9	NO_2	Me	Et	74	4	
10	NO_2	$-(CH_2)_n-$		16—71	7*a*,*b*	
11	NO_2	$-CH_2)_4O(CH_2)_5-$		88	8	
12	NO_2	H	CO_2H	90	3*c*	
13	NO_2	CO_2H	CO_2H	90	3*c*,4	
14	NO_2	H	CH_2COMe	17	9	major product 2,3-diacetyl-5-nitrocyclopenta-1,3-diene
15	CN	CO_2Et	CO_2Et		10	
16	N=NAr	H	H	51—82	11*a*,*b*	
17	N=NAr	Me	Me	74	11*a*,*b*	
18	COPh	CO_2R	CO_2R	77	12	
19	CO_2Et	CO_2R	CO_2R	50	12	
20	Ph	CO_2R	CO_2R	48	12	
21	Br	CO_2R	CO_2R	53	12	

[2] S. H. Bertz, W. O. Adams, and J. V. Silverton, *J. Org. Chem.*, 1981, **46**, 2828.
[3] (*a*) H. B. Hill and J. Torray, *Am. Chem. J.*, 1899, **22**, 892; (*b*) *ibid.*, *Chem. Ber.*, 1895, **28**, 2597; (*c*) H. B. Hill, C. A. Soch, and G. Oenslager, *Am. Chem. J.*, 1900, **24**, 1; (*d*) N. T. Hales and H. Heaney, *Tetrahedron Lett.*, 1975, 4075.
[4] E. C. S. Jones and J. J. Kenner, *J. Chem. Soc.*, 1931, 1842.
[5] (*a*) H. B. Hill, *Chem. Ber.*, 1900, **33**, 1241; (*b*) H. B. Hill and W. J. Hale, *Am. Chem. J.*, 1905, **33**, 1.
[6] T. R. Govindachari, S. Prabhakar, P. S. Santhanam, and V. Sudersanam, *Indian J. Chem.*, 1966, **4**, 433.
[7] (*a*) V. Prelog and K. Wiesner, *Helv. Chim. Acta*, 1947, **30**, 1465; (*b*) V. Prelog, K. Wiesner, W. Ingold, and O. Hafliger, *Helv. Chim. Acta*, 1948, **31**, 1325.
[8] V. Prelog, M. F. El-Neweihy, and O. Hafliger, *Helv. Chim. Acta*, 1950, **33**, 1937.
[9] W. J. Hale, *Chem. Ber.*, 1912, **45**, 1596.
[10] C. Reichardt and K. Halbritter, *Angew. Chem., Int. Ed. Engl.*, 1975, **14**, 86.
[11] (*a*) D. Leuchs, *Chem. Ber.*, 1965, **98**, 1335; (*b*) H. R. Hensel, *Chem. Ber.*, 1964, **97**, 96.
[12] V. Prelog, J. Wursch, and K. Konigsbacher, *Helv. Chim. Acta*, 1951, **34**, 258.

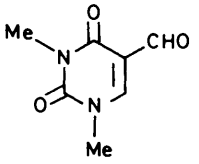
nitrophenols by conventional aromatic synthesis is so well known that it makes the ring synthesis approach rather unattractive for all but the most difficult phenols, *e.g.* entries 2, 10, and 11.

Pyrimidines such as (1)[13,14] and (2)[15,16] react with various ketones ($RCH_2C(O)CH_2R^1$) to give the corresponding 4-substituted phenols (3) in acceptable yields. The pyrimidines thus act as protected malondialdehydes as do the α,β-unsaturated aldehydes (4) which react with the dianion of ethyl acetoacetate to give the corresponding 4-substituted salicylates in good yield.[17a,b] The highly reactive fluoromalondialdehyde equivalent (5) reacts similarly to give a 4-fluorophenol with diethyl acetonedicarboxylate.[18]

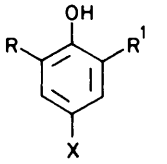


R = H, OH

(1)

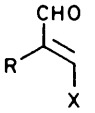


(2)



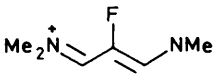
X = NO_2, CO_2R, CONHR

(3)



X = NMe_2, Cl
R = alkyl, aryl

(4)

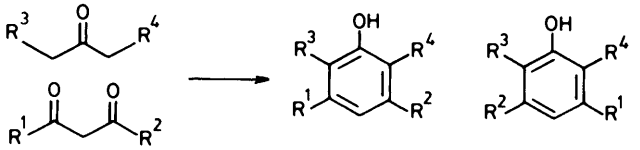


BF_4^-

(5)

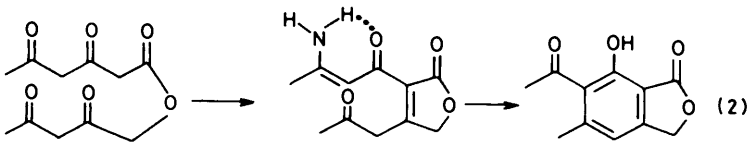
Phenols substituted at the 3/5 positions are synthesized from a ketone and either a β-ketoaldehyde or a β-diketone. Yields can be good (Table 2) though generally they tend to be lower than with malondialdehydes. Nevertheless, ketoaldehydes and diketones are usually more stable and easier to handle than malondialdehydes. They also offer a more useful alternative to conventional aromatic synthesis because of the possibilities of preparing unsymmetrical and highly substituted phenols which may be otherwise difficult to prepare. As Table 2 shows, there is considerable flexibility in the method so that various groups can be introduced into the phenol. However, a problem arises when unsymmetrical β-diketones are used since it is now possible to generate two isomers (equation 1).

[13] J. J. Fox, T.-L. Su, L. M. Stempel, and K. A. Watanabe, *J. Org. Chem.*, 1982, **47**, 1081.
[14] H. C. Van der Plas and P. Barczynski, *Recl. Trav. Chim. Pays-Bas*, 1978, **97**, 256.
[15] K. Hirota, Y. Kitade, and S. Senda, *J. Heterocycl. Chem.*, 1980, **17**, 413.
[16] K. Hirota, Y. Kitade, and S. Senda, *J. Org. Chem.*, 1981, **46**, 3949.
[17] D. H. R. Barton, G. Dressaire, B. J. Willis, A. G. M. Barrett, and M. Pfeffer, *J. Chem. Soc., Perkin Trans. 1*, 1983, 665.
[18] C. Reichardt and K. Halbritter, *Justus Liebigs Ann. Chem.*, 1975, 470.



(1)

There is no problem of course if the ketone ($R^3CH_2C(O)CH_2R^4$) is symmetrical, *e.g.* $R^3 = R^4$, entries 1—10; however, if it is not then preferential reactivity must be sought at one carbon in each of the co-reactants. One method is to employ a ketone that can be enolized preferentially in one direction and to react this with a β-dicarbonyl compound in which one carbonyl group is significantly more reactive than the other. This strategy can be seen in entries 11, 28, 33, 34—36, and 42. Preferential enolization in the ketone is achieved in many cases by incorporation of an ester group at the α-position, and for the β-diketone use can be made of the difference in reactivity between an aldehyde, an aliphatic ketone, and an aromatic ketone. Annelation of the aromatic ring to an existing ring also helps to reduce the problem of isomer formation. Equation 2 illustrates this for the preparation of a hydroxyphthalide, where the preferred formation and then reaction of an enaminoketone is utilized for final ring closure. Interestingly the 5-ring is formed *in situ* from the open chain product.[31]

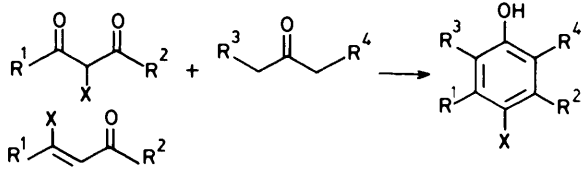


(2)

Doubly deprotonated β-ketoesters, *e.g.* $CH_2C(O)CHCO_2R$ can be silylated to give the disilylated enol diene, *e.g.* (6), which has recently been used in some acid-catalysed (regiocontrolled) syntheses of salicylates, as shown below. Once again advantage is taken of the differential reactivity at the carbon centres to achieve this control.[32a–c]

[19] (*a*) H. Muhlemann, *Pharm. Acta Helv.*, 1949, **24**, 351; (*b*) *ibid.*, p. 356.
[20] (*a*) V. Prelog, O. Metzler, and O. Jeger, *Helv. Chim. Acta*, 1947, **30**, 675; (*b*) *ibid.*, 1947, **30**, 1883.
[21] L. Ruzicka, V. Prelog, and J. Battegay, *Helv. Chim. Acta*, 1948, **31**, 1296.
[22] E. Y. Belyaev, M. S. Torbis, and A. V. El'tsov, *Zh. Org. Khim.*, 1978, **14**, 2375.
[23] G. A. Kraus, *J. Org. Chem.*, 1981, **46**, 201.
[24] N. Takeuchi, K. Ochi, M. Murase, and S. Tobinaga, *J. Chem. Soc., Chem. Commun.*, 1980, 593.
[25] (*a*) J. H. Clark and J. M. Miller, *Tetrahedron Lett.*, 1977, 139; (*b*) *ibid.*, *J. Chem. Soc., Perkin Trans. 1*, 1977, 2063.
[26] S. H. Bertz, *Synthesis*, 1980, 708.
[27] T. M. Harris, T. P. Murray, C. M. Harris, and M. Gumulka, *J. Chem. Soc., Chem. Commun.*, 1974, 362.
[28] L. Claisen, *Justus Liebigs Ann. Chem.*, 1897, **297**, 40.
[29] N. K. Kochetkov, L. J. Kudryashov, and B. P. Gottich, *Tetrahedron*, 1961, **12**, 63.
[30] (*a*) E. Belyaev, L. M. Gornostaev, A. P. Es'Kin, M. S. Torbis, G. A. Suboch, and A. V. El'tsov, *Zh. Org. Khim.*, 1977, **13**, 2307; (*b*) *ibid.*, 1978, **14**, 2189.
[31] S. Auricchio, A. Ricca, and O. V. de Pava, *Gazz. Chim. Ital.*, 1980, **110**, 567.
[32] (*a*) T. H. Chan and P. Brownbridge, *J. Am. Chem. Soc.*, 1980, **102**, 3534; (*b*) *ibid.*, *Tetrahedron*, 1981, **37**, 3387; (*c*) *ibid.*, *J. Chem. Soc., Chem. Commun.*, 1979, 578.

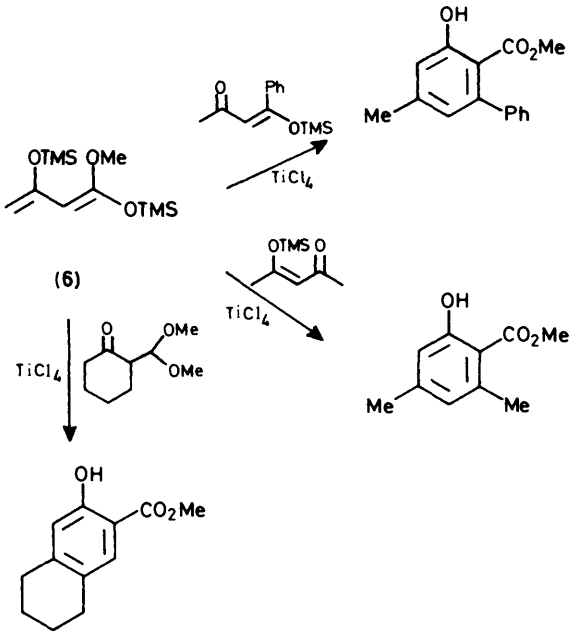
Table 2 *Condensation of ketones to give phenols*



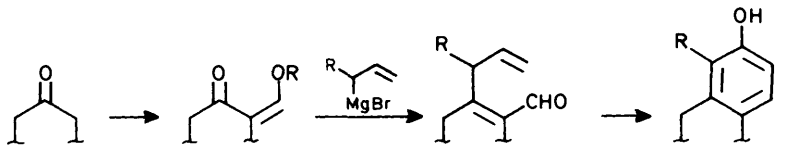
Y	X	R^1	R^2	R^3	R^4	*Yield* (%)	*Ref.*	*Comments*	*Entry*
—	H	Me	CO_2H	CO_2H	CO_2H	76	19a		1
—	H	Me	CH_2Ph	CO_2H	CO_2H	59	19b		2
—	H	Me	H	CO_2Et	CO_2Et	49	20		3
—	H	2-thienyl	H	CO_2Et	CO_2Et	61	20		4
—	H	3-pyridyl	H	CO_2Et	CO_2Et	76	20		5
—	'A' ring of steroid		H	CO_2Et	CO_2Et	57	21		6
—	N=O	Me	Me	H	H	73	22		7
—	N=NAr	Me	H	Me	Me	77	11*a,b*		8
—	N=NAr	Me	H	H	H	89	11*a,b*		9
—	N=NAr	Ph	H	Me	Me	50	11*a,b*		10
—	N=NAr	Me	H	Me	H	61	11*a,b*		11
—	H	Me	H	CO_2Me	CO_2Me	50	23		12
NMe_2	$-(CH_2)_4-$		H	CO_2Me	CO_2Me	52	24		13
NMe_2	H	Ph	H	CO_2Me	CO_2Me	23	24		14
—	H	Me	Me	H	COMe	64	25		15
—	H	$PhCH_2$	Me	CO_2Me	COMe	52	25		16
—	H	C_6H_4*p*Cl	H	CO_2Et	CO_2Et	53	12		17
—	H	C_6H_4*p*OMe	H	CO_2Et	CO_2Et	—	12		18
—	Ph	Ph	H	CO_2Et	CO_2Et	51	12		19
—	Ph	$PhCH_2$	H	CO_2Et	CO_2Et	51	12		20

—	Me	Me	H	CO_2Et	CO_2Et	52	12		21
—	H	Pr	H	CO_2Et	CO_2Et	40	12		22
—	H	Me	Me	COMe	COMe	50	26		23
—	H	Et	Me	COMe	COMe	41	26		24
—	H	Me	CF_3	COMe	COMe	13	26		25
—	H	Et	Me	CO_2Me	CO_2Me	78	26		26
—	$-(CH_2)_n-$		H	CO_2Me	CO_2Me	50—83	20		27
—	$-(CH_2)_4-$		Me	CO_2Me	CO_2Me	36	20	60% *ref.* 26	28
—	$-(CH_2)_4-$		CO_2R	CO_2Me	CO_2Me	60	26		29
—	H	Me	H	CO_2H	H	83	20		30
—	H	$C_{15}H_{31}$	H	CO_2H	CO_2H	50	20		31
—	H	Me	Me	CO_2H	CO_2H	92	20		32
—	H	Ph	H	CO_2H	CO_2H	59	20		33
—	H	Ph	Me	CO_2H	CO_2H	47	20		34
—	H	Me	H	CO_2R	H	40	27		35
OEt	CO_2Et	Me	H	H	CO_2H	63	28		36
Cl	H	Me	H	H	CO_2R	39	29		37
OMe		$(CH_2)_4$	H	H	CO_2H	—	21		38
—	N=O	Me	Me	H	H		30	3,5-dimethyl-2-nitrosophenol 23%	39
—	N=O	Me	Me	Me	H		30	3,4,5-trimethyl-2-nitrosophenol 36%	40
—	N=O	Et	Me	H	H		30	3,5,6-trimethyl-2-nitrosophenol 67%	41
—	N=O	Ar	Me	H	H	21—100	30		42
—	N=O	2-thiophenyl	Me	H	H	54	30		43
—	N=O	Ar	Me	Me	H	44—64	30		44
—	N=O	Me	Me	CO_2Me	CO_2Me	64	30		45
—	N=O	Ar	Me	CO_2Me	CO_2Me	19—25	30		46

See also—'Methoden der Organischen Chemie', Vol. 6/k pt. 2, ed. E. Muller, G. T. Verlag, Stuttgart, 1976.



The alkyl Grignard reagent $CH_2{=}C(R)CH_2MgX$ also allows the preparation of unsymmetrical phenols as demonstrated by its reaction with ketone (7), followed by an easy elaboration to the aldehyde (8). Final ring-closure then gives the phenol (9) in high yield.[33]



(7) (8) (9)

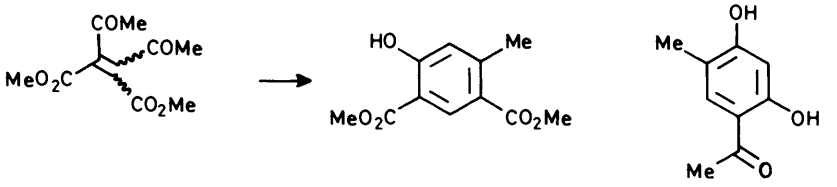
These syntheses and many of those shown in Table 2 provide synthetically useful alternatives to conventional aromatic syntheses, especially in view of the unsymmetrical substitution patterns and high levels of substitution that can be attained.

In a series of papers[34a–e] describing studies of xanthyrones and glaucyrones,

[33] M. A. Tius, A. Thurkauf, and J. W. Truesdell, *Tetrahedron Lett.*, 1982, **23**, 2823.

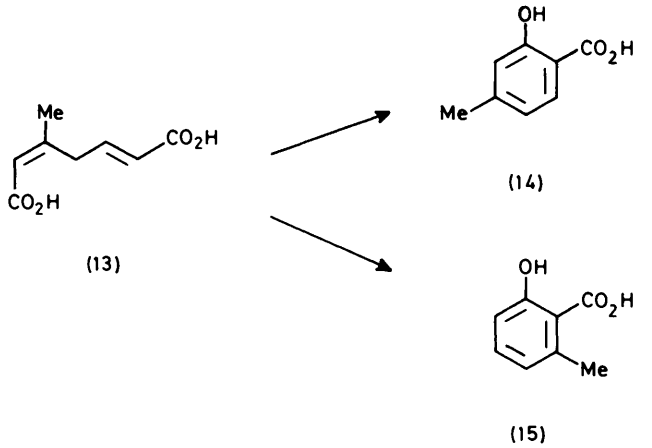
[34] (*a*) L. Crombie, D. E. Games, and A. W. G. James, *J. Chem. Soc., Perkin Trans. 1*, 1979, 464; (*b*) L. Crombie, M. Eskins, D. E. Games, and C. Loader, *J. Chem. Soc., Perkin Trans. 1*, 1979, 478; (*c*) S. R. Baker and L. Crombie, *J. Chem. Soc., Chem. Commun.*, 1980, 213; (*d*) *ibid.*, 1979, 666; (*e*) *ibid.*, 1980, 211.

Crombie and his co-workers report some useful reactions leading to phenols containing acetyl, ester, alkyl, and alkene groups. Strong chelation effects are observed in many of these reactions and as an example the compound (10) cyclizes exclusively to the salicylate (11) with sodium ethoxide (see also Claisen[35]) or magnesium methoxide and not at all to the resorcinol (12); however, in an excess of magnesium methoxide mixtures of both result.



(10) (11) (12)

Zinc chloride can also play an important role in determining the direction of cyclization. Thus, in its absence, ring-closure of the diacid (13) occurs to the salicylic acid (14) whereas with $ZnCl_2$ present the salicylic acid (15) is formed.[36]

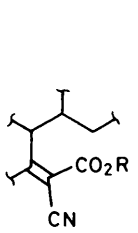


(13) (14) (15)

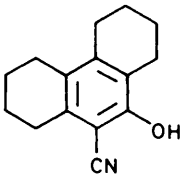
The above example illustrates an alternative source of the phenolic oxygen, *i.e.* from a carboxylic acid, and contrasts with the syntheses already discussed. Continuing in a similar vein, cyclization onto an ester [*e.g.* (16)] gives rise to the cyanophenols (17)[37] and (18)[38] and by a similar strategy the highly substituted cyanophenols (19)[39] and (40)[40] are obtained in fair yields. These latter syntheses

[35] L. Claisen, *Justus Liebigs Ann. Chem.*, 1897, 2971.
[36] G. Agnes and G. P. Chiusoli, *Chim. Ind.* (*Milan*), 1967, **49**, 465.
[37] J. Sepiol and J. Mirek, *Synthesis*, 1979, 290.
[38] O. S. Wolfbeis, G. Zacharias, and H. Junek, *Monatsh. Chem.*, 1975, **106**, 1207.
[39] (*a*) T. Severin, B. Bruck, and P. Adhikary, *Chem. Ber.*, 1966, **99**, 3097; (*b*) T. Severin and B. Bruck, *Angew. Chem., Int. Ed. Engl.*, 1964, **3**, 806.
[40] C. Ivanov and T. Tcholakova, *Synthesis*, 1982, 730.

are particularly useful because of the ease of synthesis and availability of the precursors, and also because of the degree and nature of the substitution pattern which would not be easy to achieve by alternative processes. A similar strategy is apparent in the synthesis of cyanoanilines (see Section 4).



(16)



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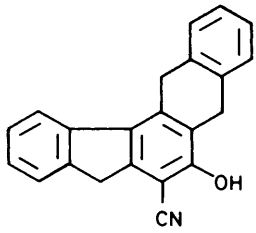

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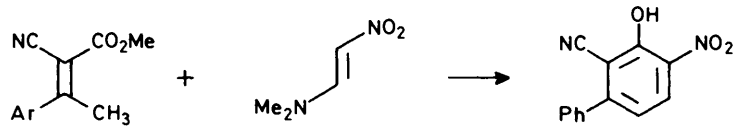

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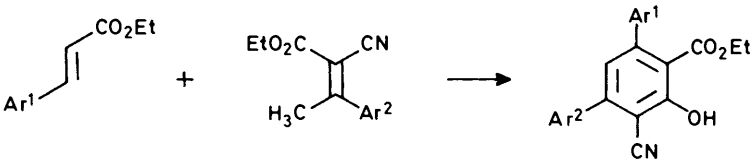
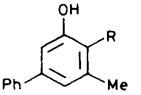
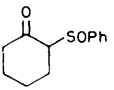
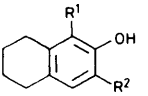
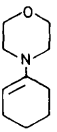
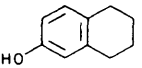
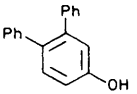
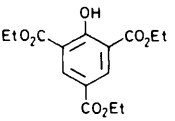
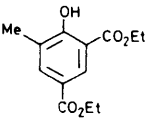
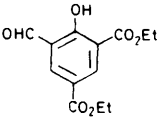
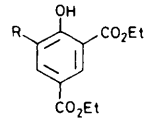
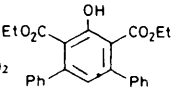


(20)

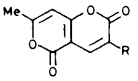
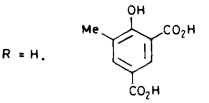
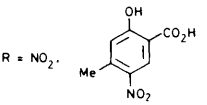
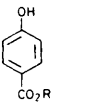
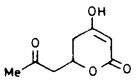
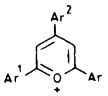
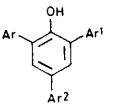
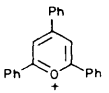
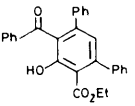
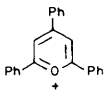
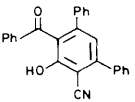
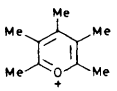
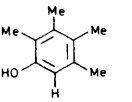
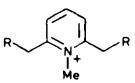
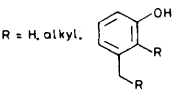
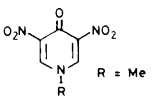
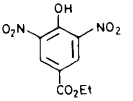
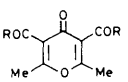
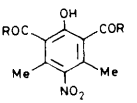
The last two examples illustrate the use of Michael acceptors and further examples are shown in Table 3. The variety and, in many cases, cheapness of these versatile reagents makes them very useful for aromatic-ring synthesis and greatly increases the utility of the method. In many cases an eliminatable group, *e.g.* SOPh, halogen, OR, must be present in one of the acyclic precursors to ensure aromatization, otherwise only a cyclohexenone is formed. The eliminatable group can also play a second role, in that it can control the regiochemistry of condensation. See entries 1 and 2 in Table 3 where the sulphoxide group fulfils the dual role of directing the reaction and then eliminates to form the phenol. If an acetylene is used, entry 6, then there is no need for an eliminatable group, although this modification is of limited use since acetylenes themselves, with a few exceptions, are neither cheap nor readily available. This route is therefore only likely to be of use for more inaccessible phenols.

Table 3 *Phenols from Michael acceptors*

Entry	*Michael Acceptor*	*Co-reactant*	*Product*	*Yield* %	*Ref.*
1	PhCH=CHCOMe	$PhSOCH_2COCH_2R$		R = H 62 R = Et 50	41
2	$CH_2=C(R^2)COCH_2R^1$			R^1 = H, Me30,58 R^2 = H, Me, Ar	42
3	$CH_2=C(F)COMe$				43
4	$CH_2=CHCOMe$	$PhC(OH)C(O)Ph$			44
5	$EtOCH=CHCO_2Et$	$CH_2(CO_2Et)_2$		14	45*a*
6	$EtOCH=CHCO_2Et$	$MeCH(CO_2Et)_2$		47	45*a*
7	$EtOCH=CHCO_2Et$			48	45*a*
8	$EtOCH=C(CO_2Et_2)$	RCH_2CO_2Et		R = Ph 24 R = 2-thienyl 12 R = 3-pyridyl 61	45*b*
9	$PhC\equiv CCOPh$	$O=C(CH_2CO_2Et)_2$		40	46

[41] A. A. Jaxa-Chamiec, P. G. Sammes, and P. D. Kennewell, *J. Chem. Soc., Perkin Trans. 1*, 1980, 170.
[42] D. L. Boger and M. D. Mullican, *J. Org. Chem.*, 1980, **45**, 5002.
[43] H. Molines and C. Wakselman, *J. Chem. Soc., Chem. Commun.*, 1975, 232.
[44] C. Egli, S. E. Helali, and E. Hardegger, *Helv. Chim. Acta*, 1975, **58**, 104.
[45] (*a*) W. J. Croxall and M. F. Fegley, *J. Am. Chem. Soc.*, 1950, **72**, 970; (*b*) C. W. Bird and C. K. Wong, *Tetrahedron Lett.*, 1975, 1877.
[46] W. Deuschel, *Helv. Chim. Acta*, 1951, **34**, 168.

Table 4 *Phenols from six-membered ring heterocycles*

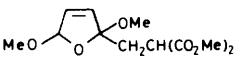
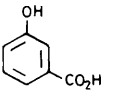
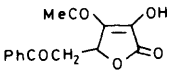
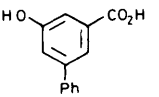
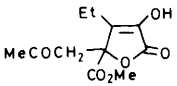
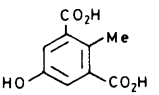
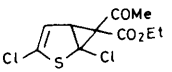
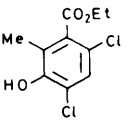
Entry	*Heterocycle*	*Co-reactant*	*Product*	*Yield %*	*Ref.*
1			 R = H.	50	47
2			 R = NO_2.	30	47
3		$CH_2(CO_2R)_2$		—	48
4				30	49
5		$MeNO_2$		22—78	50
6		$CH_2(CO_2Et)_2$		27	51
7		$CH_2(CN)CO_2Et$		37	52
8				46	53
9			 R = H, alkyl.	70—80	53
10	 R = Me	$MeC(O)CH_2CO_2Et$		65—72	54
11		$MeNO_2$		77—80	55

Heterocyclic systems have already been shown to be a useful source of phenols by ring cleavage. Several oxygen heterocycles are particularly susceptible to hydrolysis and nucleophilic attack as shown in Table 4 and provide some useful routes to highly functionalized benzenoids, although the yields are at best only mediocre in the examples illustrated.

Pyridinium salts are also susceptible to cleavage and, as Table 4 shows, they provide a route to phenols, although the scope is limited in the example shown. Nevertheless further extensions might be possible. The preparation of 2,3,4,5-tetramethylphenol is claimed to be a feasible alternative to conventional synthesis but, on the whole, syntheses based upon pyrylium salts are likely to be most useful for rather inaccessible phenols. (Entry 8.)

It is less common to find five-membered heterocycles as a source of phenols, with what few examples there are being dominated by oxygen heterocycles (Table 5). Interestingly, all the examples shown are to *m*-carboxyphenols; this complements the syntheses of *o*/*p* carboxyphenols already described in earlier tables.

Table 5 *Phenols from five-membered ring heterocycles*

Heterocycle	*Product*	*Yield* %	*Ref.*	*Entry*
		26	56	1
		—	57	2
		68	58	3
		86	59	4

[47] F. C. Cheng and S. F. Tan, *J. Chem. Soc. C*, 1968, 543.
[48] E. D. Bergman, D. Ginsburg, and R. Pappo, *Org. React.*, 1959, **10**, 179.
[49] H. Guilford, A. I. Scott, D. C. Skingle, and M. Yalpani, *J. Chem. Soc., Chem. Commun.*, 1968, 1127.
[50] K. Dimroth and H. Wache, *Chem. Ber.*, 1966, **99**, 399.
[51] (*a*) K. Dimroth and G. Neubauer, *Angew. Chem.*, 1957, **69**, 720; (*b*) *ibid.*, *Chem. Ber.*, 1959, **92**, 2046.
[52] H. G. Rajoharison, H. Soltani, M. Arnaud, C. Roussel, and J. Metzger, *Synth. Commun.*, 1980, **10**, 195.
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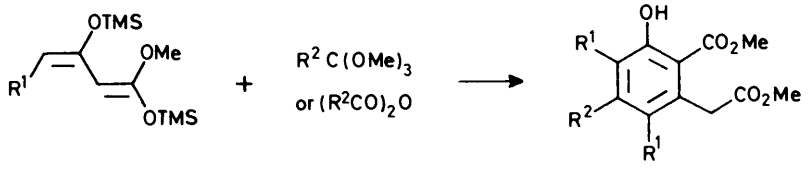
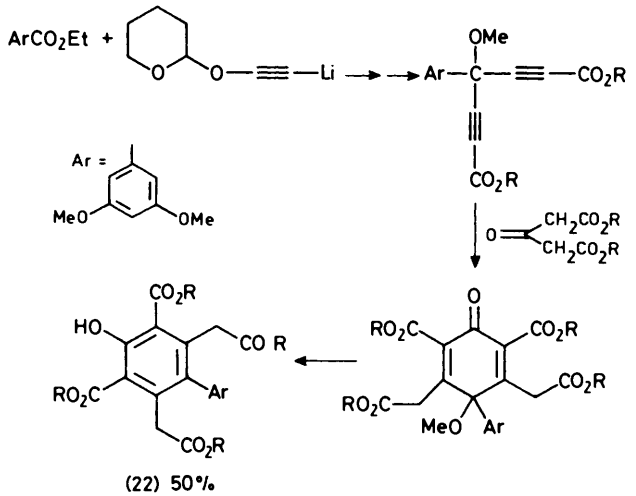
[55] F. Eiden, H. P. Leister, D. Mayer, *Arzneim-Forsch.*, 1983, **33**, 101.
[56] N. Elming, *Acta Chem. Scand.*, 1956, **10**, 1664.
[57] A. Bianco, M. L. Scarpati, and C. Trogolo, *Ann. Chim. (Rome)*, 1972, **62**, 709.
[58] C. Iavarone, M. L. Scarpati, and C. Trogolo, *Gazz. Chim. Ital.*, 1971, **101**, 748.
[59] R. J. Gillespie, J. Murray-Rust, P. Murray-Rust, and A. E. A. Porter, *Tetrahedron*, 1981, **37**, 743.

Some of the syntheses already highlighted have been used in routes to natural products. Similarly, sclerin and resistomycin have both been synthesized recently and depend upon a ring-synthesis method to build up the phenol ring. In the synthesis of sclerin a general synthesis of 3-hydroxyphthalides (21) was developed,[60] and for resistomycin the biphenyl (22) was elegantly elaborated.[61] In both cases the ring synthesis approach is superior to that of the conventional approach.



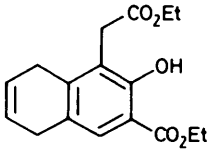
(21)



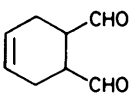
(22) 50%

A further example of phenylacetic ester formation is illustrated in the preparation of the phenol (23, 40%) from the dialdehyde (24) and involves a rearrangement; the mechanism is proposed in the paper.[62] In a quite intriguing reaction, pentane-1,3-dione condenses with maleic anhydride to give a fair yield (50%) of the internally protected phenol (25),[63] and oxalyldialdehyde condenses with nitromethane to provide the acetyl derivative of 2,4-dinitrophenol.[64] More simply the decalenone (26) undergoes a ready rearrangement to the phenol (27).[65]

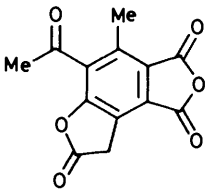
[60] T. H. Chan and P. Brownbridge, *J. Chem. Soc., Chem. Commun.*, 1981, 20.
[61] K. James and R. A. Raphael, *Tetrahedron Lett.*, 1979, 3895.
[62] D. S. Tarbell and B. W. Hargotz, *J. Am. Chem. Soc.*, 1954, **76**, 5761.
[63] E. Berner, *J. Chem. Soc.*, 1946, 1052.
[64] F. W. Lichtenthaler, *Angew. Chem., Int. Ed. Engl.*, 1964, **73**, 211.
[65] M. Kalyanasunderam, K. Rajagopalan, and S. Swarminathan, *Tetrahedron Lett.*, 1980, **21**, 4391.



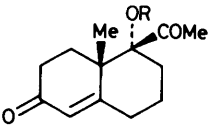
(23)



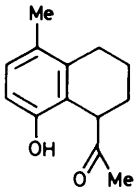
(24)



(25)



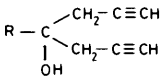
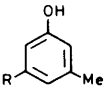
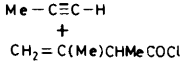
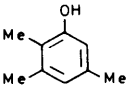
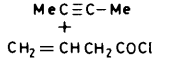
(26)

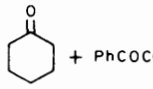
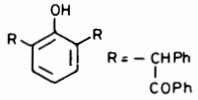
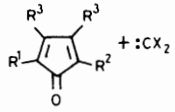
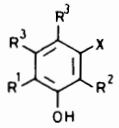
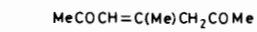
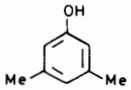


(27)

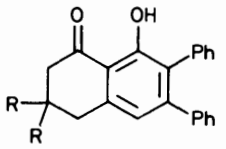
It is less common to find ring syntheses of phenols containing no acceptor groups whatever; however, the versatility of the method is such that it is nearly always possible to find a ring synthesis approach to any general class of phenol. This can be illustrated by the phenols in Table 6 which contain only alkyl, aryl, or halogeno substituents. Some of these examples appear fairly general, yields are fair and access is provided to some particularly difficult phenols, *e.g.* polyarylated phenols. The method is only limited in some cases by the inaccessibility of the starting materials.

Table 6 *Alkyl-, aryl-, and halogeno-substituted phenols*

Precursors	*Phenol*	*Yield %*	*Ref.*
		R = H 35 Me 50 Et 34 Pr^{i} 39 Bu^{t} 40	66
		67	67
		39	67

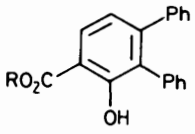
Precursors	*Phenol*	*Yield %*	*Ref.*
		20	68
		R^3 = aryl R^1R^2 = alkyl aryl 55—89 X = Cl, Br	69
			70

Diphenylcyclopropenone reacts with carbon ylides to give, for example, diphenyl phenols (28)[71] and (29).[72] However, despite the satisfactory yields and unusual substitution pattern the high cost of diphenylcyclopropenone seriously limits the usefulness of this route. Similarly, the cycloheptenone (30) is a rather exotic precursor to *m*-hydroxybenzaldehyde (85%) and is of more mechanistic than synthetic interest.[73]

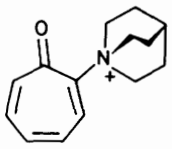


R = H, Me

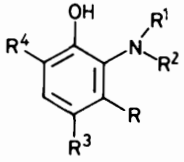
(28)



(29)



(30)



R = H, Me, Ar

R^3 = H, Me

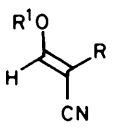
R^4 = H, Me

(31)

[66] D. Plouin and R. Glenat, *Bull. Soc. Chim.*, 1975, 336.
[67] M. Karpf, *Tetrahedron Lett.*, 1982, **47**, 4923.
[68] C. F. H. Allen and J. A. Van Allen, *J. Org. Chem.*, 1951, **16**, 716.
[69] K. Steinbeck, T. Schenke, and J. Runsink, *Chem. Ber.*, 1981, **114**, 1836.
[70] A. Baeyer and J. Piccard, *Justus Liebigs Ann. Chem.*, 1915, **407**, 332.
[71] Y. Tamura, T. Miyamoto, H. Kiyokawa, and Y. Kita, *J. Chem. Soc., Perkin Trans. 1*, 1974, 2053.
[72] T. Sasaki, K. Kanematsu, A. Kahehi, and G. Ito, *Tetrahedron*, 1972, **28**, 4947.
[73] G. Biggi, A. J. de Hoog, F. D. Cima, and F. Pietra, *J. Am. Chem. Soc.*, 1973, **95**, 7108.

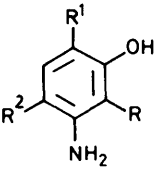
All the reactions thus far concern the synthesis of phenols containing alkyl, aryl, and electron-withdrawing groups. However, it is just as feasible to introduce donor groups by ring synthesis methods and aminophenols are an important case in point. For instance *o*-aminophenols (31) can be prepared from the corresponding 2-acylfuranone and a cyclic amine, albeit in rather variable yields.[74] This method is of limited utility in view of the ready synthesis of *o*-aminophenols by conventional methods. In general the synthesis of *m*-aminophenols has received more attention in the literature and proves to be far more useful. Various *m*-aminophenols containing carboxylic acid, cyano, alkyl, acyl, and halogeno groups can be readily synthesized from simple and available acyclic precursors. The level of substitution can also be varied as can the substitution pattern.

Furthermore, the products in many cases are not easily accessible by conventional aromatic synthesis. For example, the ethoxymethylene compounds (32) condense with active methylene compounds, *e.g.* β-ketoesters, malononitrile, cyanoacetic ester, to yield the corresponding *m*-aminophenols (33) in good yields.[75–77] Enamine (34) reacts with 1,2-dibromoacryloyl chloride to give the *m*-aminophenol (35),[78] whereas enamines (36) dimerize to provide (37).[79,80] However, dimerization can be prevented if a silyl group is included in the enamine such as in (38),[81] thus allowing cross-condensation between enamines. Interestingly, the direction of cyclization depends upon the nature of the co-reacting enamine so that enamines derived from acyclic ketones give aminophenols (39) by 3C + 3C addition, and enamines derived from cyclic ketones (n = 2—5) give aminophenols (40) by 4C + 2C addition. If $n > 5$ then 3C + 3C addition occurs once again.



R = CN, CO_2Me

(32)

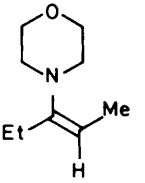


R = H, CO_2R, alkyl

R^2 = CN, CO_2R

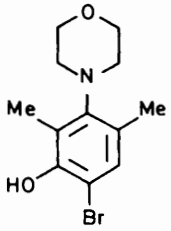
R^1 = COMe, CO_2R

(33)

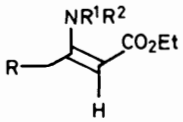


(34)

[74] (*a*) L. Birkofer and G. Daum, *Angew. Chem.*, 1960, **72**, 707; (*b*) *ibid.*, *Chem. Ber.*, 1962, **95**, 183.
[75] H. W. Schmidt and H. Junek, *Justus Liebigs Ann. Chem.*, 1979, 2005.
[76] S. R. Baker, L. Crombie, R. V. Dove, and D. A. Slack, *J. Chem. Soc., Perkin Trans. 1*, 1979, 677.
[77] D. Leaver and J. D. R. Vass, *J. Chem. Soc.*, 1965, 1629.
[78] (*a*) P. W. Hickmott, B. J. Hopkins, and C. T. Yoxall, *Tetrahedron Lett.*, 1970, **29**, 2519; (*b*) N. F. Firrel, P. W. Hickmott, and B. J. Hopkins, *J. Chem. Soc.*, 1970, 1477.
[79] I. A. Zaitsev, M. M. Shestaeva, and V. A. Zagorevskii, *Zh. Org. Khim.*, 1966, **36**, 1769.
[80] H. Bohme, J. G. von Gratz, F. Martin, R. Matusch, and J. Nehne, *Justus Liebigs Ann. Chem.*, 1980, 394.
[81] T. H. Chan and G. J. Kang, *Tetrahedron Lett.*, 1983, **24**, 3051.

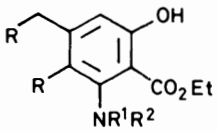


(35)

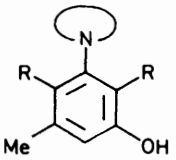


R = H, Me, Ph

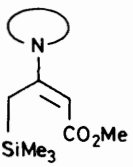
(36)



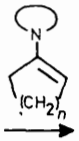
(37)

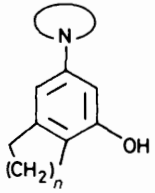


(39)



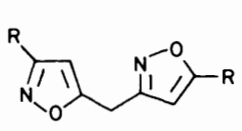
(38)



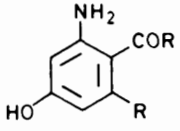


(40)

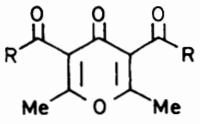
In common with other phenols described earlier aminophenols can also be prepared from heterocycles as shown by the conversion of dioxazoles (41) into aminophenol (42).[82] Potentially more useful is the facile acylpyrone–phenol rearrangement of (43) to (44) which is usually accomplished in good yield.[83a–e]



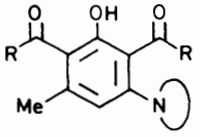
(41)



(42)



(43)



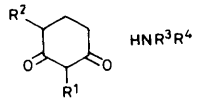
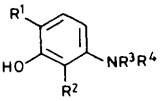
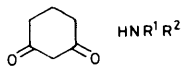
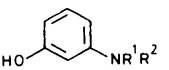
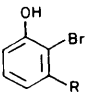
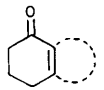
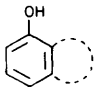
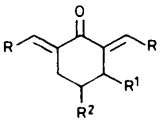
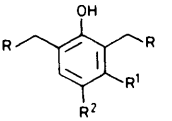
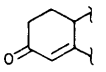
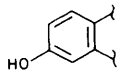
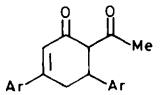
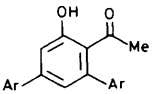
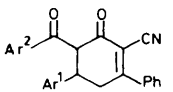
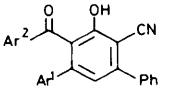
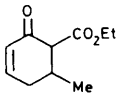
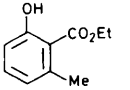
(44)

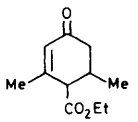
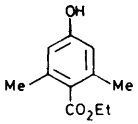
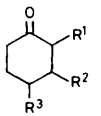
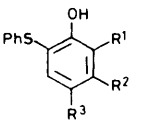
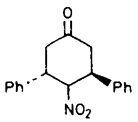
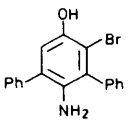
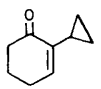
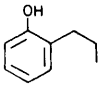
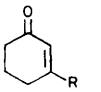
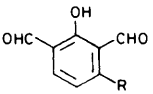
[82] S. Auricchio, S. Morrocchi, and A. Ricca, *Tetrahedron Lett.*, 1974, 2793.

[83] (*a*) F. Eiden, E. G. Teupe, H. P. Leister, and D. Mayer, Patent, Ger. Offen 2 922 488 (*Chem. Abstr.*, 1981, **94**, 191 938); (*b*) F. Eiden, E. G. Teupe, and H. P. Leister, *Arch. Pharm.*, 1981, **314**, 419; (*c*) *ibid.*, p. 347; (*d*) F. Eiden and H. P. Leister, *Arch. Pharm.*, 1980, **313**, 972; (*e*) F. Eiden and E. G. Teupe, *Arch. Pharm.*, 1979, **312**, 591.

All the syntheses have so far involved condensations, additions, and cyclizations leading directly to the aromatic compound, *i.e.* there is sufficient potential unsaturation in the acyclic precursors to generate the aromatic ring directly. However, there is substantial literature precedent for aromatizing cyclohexenones, cyclohexanones *etc.*, and various reagents and procedures are available. Since many cyclohexanone/enones are available this is a method well worth considering as a feasible alternative to conventional routes, see Table 7. Only a small cross-section of examples is included since this topic is outside the scope of this review.

Table 7 *Phenols by aromatization reactions*

Entry	*Precursors*	*Reagent*	*Product*	*Yield %*	*Ref.*
1		$Hg(OAc)_2$		32—79	84
2		−[H]		—	85
3		Br_2–NaOH		10—60	86
4		Me_3SiCl–DDQ		25—95	87
5		$IrCl(CO)(PPh_3)_2$			88
6		CuBr–LiBr		80	89
7					90*a*,*b*
8		S		12—62	91
9		Br_2–AcOH		82	92

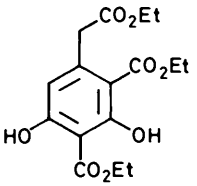
Entry	*Precursors*	*Reagent*	*Product*	*Yield %*	*Ref.*
10		Br_2–CS_2		45	93
11		PhSSPh–NaOMe		42—79	94
12		HBr–AcOH		40	95
13		300 °C		65	96
14		HCO_2Et		10—28	97

B. Dihydroxybenzenes.—Perhaps not surprisingly the strategy for the preparation of dihydroxybenzenes (catechols, resorcinols, and quinols) bears a strong resemblance to that just described for phenols. As before, the aromatic hydroxy-groups usually come from carbonyl groups and once again the Aldol and Michael reactions are important. However, the Claisen condensation is used far more in the preparation of dihydroxybenzenes than for phenols and is found in many syntheses either at the ring-closure stage or in the assembly of the precursors prior to final ring-closure. Furthermore, many of the ketones, esters, ketoesters, and their unsaturated derivatives used in the synthesis of phenols can also be used for the preparation of dihydroxybenzenes.

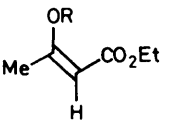
[84] H. Ida, Y. Yuasa, and C. Kibayashi, *Synthesis*, 1982, 471.
[85] W. H. Mueller, Patent, U.S. 4 212 823 (*Chem. Abstr.*, 1980, **93**, 239 028).
[86] S. R. Ramadas, D. Rau, and W. Sucrow, *Chem. Ber.*, 1980, **113**, 2579.
[87] M. T. Reetz and W. Stephan, *Justus Liebigs Ann. Chem.*, 1980, 533.
[88] Y. Pickholtz, Y. Sasson, and J. Blum, *Tetrahedron Lett.*, 1974, 1263.
[89] D. Boudon, Y. Pietrasanta, and B. Pucci, *Tetrahedron Lett.*, 1977, 821.
[90] (*a*) M. A. Elhashash, A. A. Afify, and A. Nagy, *Indian J. Chem., Sect. B*, 1979, **17**, 581; (*b*) M. Abdalla, M. A. I. Salem, and A. Hataba, *Rev. Roum. Chim.*, 1980, **25**, 1335.
[91] C. Ivanov and T. Tcholakova, *Synthesis*, 1981, 392.
[92] F. M. Hauser and S. A. Pogany, *Synthesis*, 1980, 814.
[93] K. K. Bhattacharya, P. Pal, K. Ghosh, and P. K. Sen, *Indian J. Chem., Sect. B*, 1980, **19**, 191.
[94] B. M. Trost and J. H. Rigby, *Tetrahedron Lett.*, 1978, 1667.
[95] D. W. Theobald, *Tetrahedron*, 1983, **39**, 1605.
[96] G. Pattenden and D. Whybrow, *J. Chem. Soc., Perkin Trans. 1*, 1981, 3147.
[97] S. Labidalle, E. Jean, H. Moskowitz, H. Miocque, and C. Thal, *Tetrahedron Lett.*, 1981, **22**, 2869.

In this category, syntheses of resorcinols are the most commonly found in the literature and many prove to be useful alternatives to conventional methods. Several reports have appeared pertaining to the synthesis of natural products containing the resorcinol ring and activity in this area is likely to continue in view of the physiological activity of resorcinol derivatives, *e.g.* benzochromans.

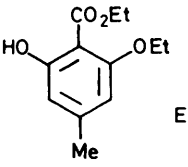
Simple dimerization of β-ketoesters can lead to interesting resorcinols. For instance diethyl acetonedicarboxylate dimerizes to the highly substituted resorcinol (45)[98a,b] and the enol ether of ethyl acetoacetate (46) undergoes $TiCl_4$-catalysed dimerization to the monoethyl ether of a resorcinol.[99] Interestingly, the nature of the enol ether is critical in deciding the final product since (46, R = Et) yields the 2-substituted resorcinol (47) whereas (46, R = Ph) yields the 2-unsubstituted resorcinol (48). In both cases, the formation of the monoether is specific with no diether formation and no isomer mixtures.



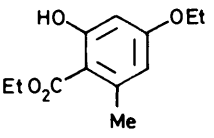
(45)



(46)



(47)



(48)

The disubstituted resorcinol (49), has been the subject of successful synthetic studies as shown in Scheme 1. Several routes provide good alternatives to conventional syntheses and show elegant use of dianions, and their silyl derivatives, in regiospecific condensations.[100-104]

2-Substituted resorcinols are also easily made and this can be illustrated by the synthesis of the resorcinol (50) from the silyl derivative (51) and the ketalester (52).[105] This reaction contrasts with one shown in Scheme 1 [to give the 2-unsubstituted (49)[105]] and demonstrates the control that can be exercised in these condensations by careful manipulation of reactive groups. Continuing upon this theme, ethyl acetoacetate condenses with diethyl acetonedicarboxylate to give resorcinol (53), which again shows that cross-condensations as well as

[98] (*a*) H. Cornelius and H. von Pechman, *Chem. Ber.*, 1886, **19**, 1446; (*b*) D. S. Jerdan, *J. Chem. Soc.*, 1899, **75**, 808.

[99] G. Declerq, G. Moutardier, and P. Mastagli, *C.R. Hebd. Seances Acad. Sci., Ser. C*, 1975, **281**, 279.

[100] (*a*) T. A. Hase, E. Suokas, and K. McCoy, *Acta Chem. Scand., Ser. B*, 1978, **32**, 701; (*b*) T. Kato, M. Sato, and T. Hozumi, *J. Chem. Soc., Perkin Trans. 1*, 1979, 529; (*c*) T. Kato and T. Hozumi, *Chem. Pharm. Bull.*, 1972, **20**, 1574.

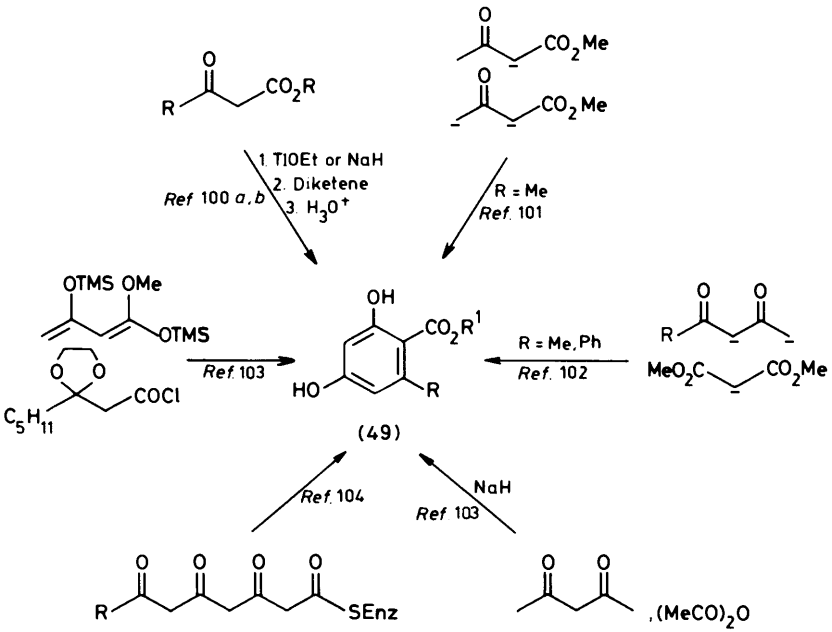
[101] (*a*) S. N. Huckin and L. Weiler, *Can. J. Chem.*, 1974, **52**, 1343; (*b*) P. E. Sum and L. Weiler, *J. Chem. Soc., Chem. Commun.*, 1977, 91.

[102] J. E. Hill and T. M. Harris, *Synth. Commun.*, 1982, 621.

[103] A. G. M. Barrett, T. M. Morris, and D. H. R. Barton, *J. Chem. Soc., Perkin Trans. 1*, 1980, 2272.

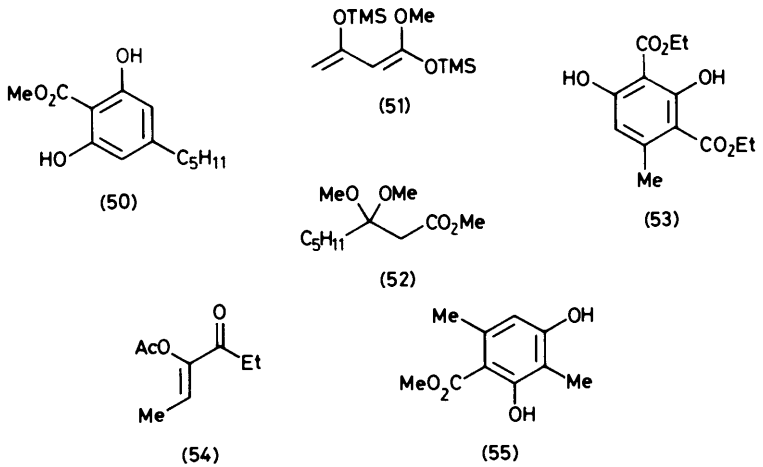
[104] T. M. Harris and C. M. Harris, *Tetrahedron*, 1977, **33**, 2159.

[105] T. H. Chan and T. Chaly, *Tetrahedron Lett.*, 1982, **23**, 2935.



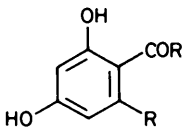
Scheme 1

dimerizations are possible,[106] and dimethylmalonate condenses with the α,β-unsaturated ketone (54) to yield the 2-methylresorcinol (55).[107]

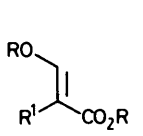


[106] G. Koller and E. Krakauer, *Monatsh. Chem.*, 1929, **53—54**, 931.
[107] K. K. Light, Patent, U.S. 3 928 419; *Chem. Abstr.*, 1976, **84**, 105 224.

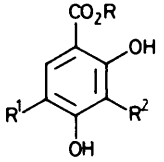
The ketone analogues of resorcinolester (49) are also available from acyclic precursors, as can be seen in the preparation of resorcinols (56)[82,108] from open-chain keto-compounds.



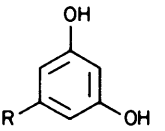
(56)



(57)



(58)

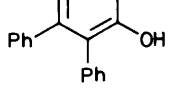


R = alkyl, aryl, heterocyclyl

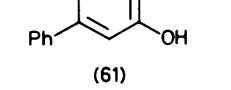
(59)

Various substituted resorcinols can be prepared from alkoxymethylene compounds (57). For example, (57, R^1 = CN) yields the cyanoresorcinol (58, R^1 = CN, R = CO_2R) when reacted with acetonedicarboxylic esters,[77] whereas the ketoresorcinol (58, R^1 = COR, R = H) is formed from (57, R^1 = COR) and ethyl acetoacetate.[34a,109] Similarly, diethyl acetonedicarboxylate reacts with 2-dimethylaminonitroethylene to provide the nitroresorcinol (58, R^1 = NO_2, R^2 = H).[39] Because of the simplicity and availability of these precursors and the highly substituted compounds that can be obtained, these routes constitute very attractive and convenient methods for synthesizing resorcinols. Alkylresorcinols can be prepared by hydrolysing and decarboxylating the corresponding resorcinol esters. However, a particularly convenient direct route involves the reaction between methyl phenylsulphinylacetate and various substituted α,β-unsaturated ketones; the orcinols (59) are obtained generally in moderate yield.[41]

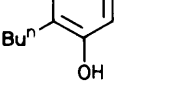
The need for an eliminatable group when using the Michael reaction in ethylene compounds is obviated when acetylenes are used since the precursors already possess the correct level of unsaturation for the final aromatization. Thus, conjugated acetylene compounds (R–C≡C–COR^1) react with 1,1′-diphenylacetone to give resorcinols (60),[110] with diethyl acetonedicarboxylate to yield (61),[111] and with diethyl malonate to provide resorcinols (62).[112] The yields are moderate but in



(60)



(61)

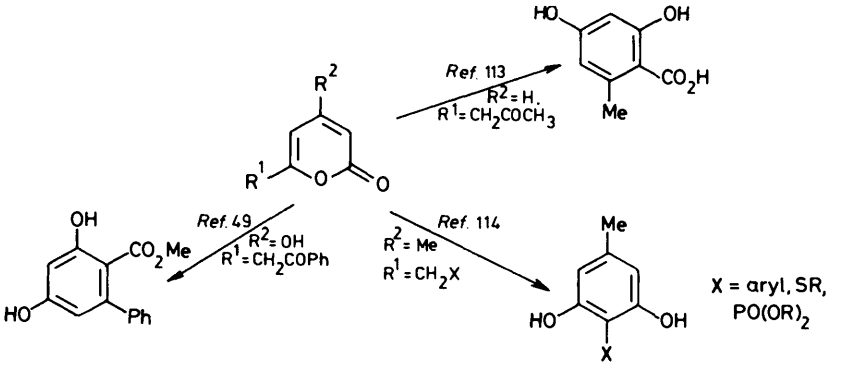


(62)

[108] H. Zak and U. Schmidt, *Chem. Ber.*, 1973, **106**, 3652.
[109] L. Crombie, D. E. Games, and A. W. G. James, *J. Chem. Soc., Perkin Trans. 1*, 1979, 472.
[110] I. El-Kholy, M. M. Mishrikey, F. K. Rafla, G. Soliman, *J. Chem. Soc.*, 1962, 5153.
[111] Patent, D.O.S. 1973, 2 359 410.
[112] (*a*) R. M. Anker and A. H. Cook, *J. Chem. Soc.*, 1945, 311; (*b*) J. C. Bardhan, *J. Chem. Soc.*, 1929, 2223; (*c*) E. P. Kohler, *J. Am. Chem. Soc.*, 1922, **44**, 379; (*d*) L. Bickel, *J. Am. Chem. Soc.*, 1950, **72**, 1022.

view of the limited availability, and in many cases the inaccessibility of useful acetylene compounds, this method is only likely to be of use for less easily obtainable resorcinols.

As with phenols, certain oxygen heterocycles can be easily converted into resorcinols after ring cleavage. Scheme 2 demonstrates this for lactones. Another

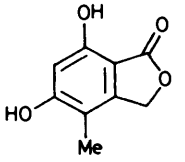


Scheme 2

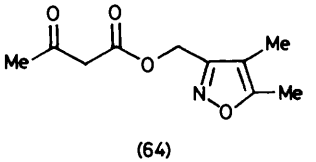
lactone, dehydroacetic acid, is converted into 5-methylresorcinol simply by heating in water; this reaction was discovered some 90 years ago.[115]

Isoxazolines have already been shown to be useful in the preparation of aminophenols and phenols and the same author has utilized them for the synthesis of dihydroxy-phthalides (63) in three simple steps from (64) in an overall yield of 20%.[116] The phthalide (63) can then be converted into mycophenolic acid.

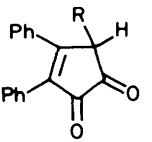
The cyclopentenedione (65) provides another example of a regiocontrolled reaction with either the resorcinol (66) or the catechol (67) formed, according to the



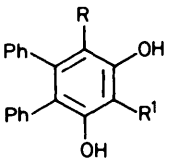
(63)



(64)



(65)



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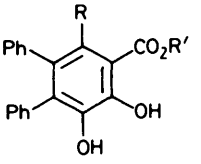
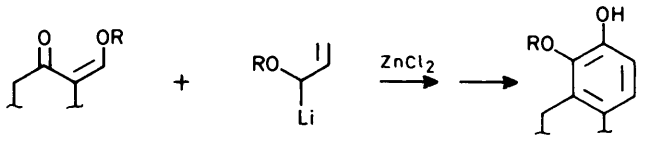


(67)

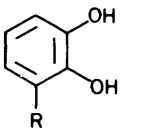
[113] R. Bentley and P. W. Zwitkowits, *J. Am. Chem. Soc.*, 1967, **89**, 676.
[114] Patent, Fr. Demande, 410 795; *Chem. Abstr.*, 1966, **64**, 3423.
[115] N. Collie and W. S. Myers, *J. Chem. Soc.*, 1893, **63**, 122.
[116] S. Auricchio, A. Ricca, and O. V. de Pava, *J. Org. Chem.*, 1983, **48**, 602.

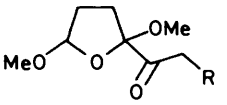
reagents and conditions used.[117] Thus, (66) is preferentially formed when diazo-compounds (R^1CHN_2, R^1 = COPh, H, or Br) are used with zinc chloride catalysis, whereas (67) is favoured when $N_2CH_2CO_2R$ is the co-reactant and no catalyst is present.

In general, far fewer references are available to the preparation of catechols; however, a useful general method for preparing substituted catechol monoethers (68) has been reported by Tius,[118] as shown below, and proceeds in moderate to good yields. Mono-ethers of catechol have also been prepared by treating 2,2,6-trichlorohexanone with alcohols and base.[119] Both these methods are useful because of the easy and selective formation of the mono-ethers which can be troublesome to prepare by direct alkylation of catechols.



(68)





R = H, alkyl, acetyl

(69) (70)

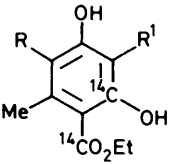
3-Substituted catechols (69) are made upon treatment of the saturated furan (70);[120] the yields are rather poor and the method would therefore seem to be of limited use.

Hydroquinone can be made in very high yield by the action of acetic anhydride and mineral acid upon the cyclohexa-1,4-dione.[121] However, no indication of whether this reaction is generally applicable is given, although catechol and resorcinol can also be synthesized in very high yield from the corresponding diketones. 2,5-Dimethylquinol is obtained by dimerization of butane-2,3-dione in 30% yield, but once again no indication is given of the generality of the reaction.[122]

Just as for phenols, dihydroxybenzenes can be obtained by aromatization. The

[117] B. Eistert and E. A. Hackmann, *Justus Liebigs Ann. Chem.*, 1962, **657**, 120.
[118] M. A. Tius and A. Thurkauf, *J. Org. Chem.*, 1983, **48**, 3839.
[119] Van Winckel, Patent, U.S. 4 267 388.
[120] (*a*) W. R. Boehme, *J. Am. Chem. Soc.*, 1960, **82**, 498; (*b*) J. T. Nielson, N. Elming, and N. Clauson-Kaas, *Acta Chem. Scand.*, 1955, **9**, 9.
[121] M. S. Kablaoui, *J. Org. Chem.*, 1974, **39**, 3696.
[122] Patent, Ger., 1 220 437; *Chem. Abstr.*, **65**, 10531.

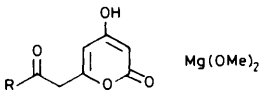
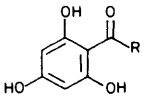
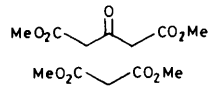
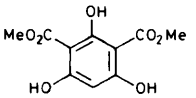
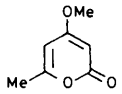
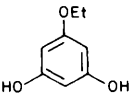
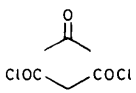
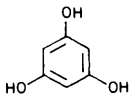
aromatization to quinone just described is such an example,[121] and another is the synthesis of doubly labelled resorcylic esters (71) which are obtained by condensation of $MeCH{:}CRCOCH_2R^1$ with $CH_2(^{14}CO_2Et)_2$ followed by dehydrogenation.[123] Many further examples are to be found in the literature.



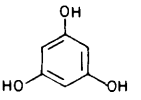
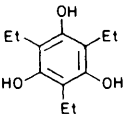
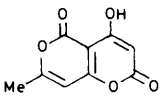
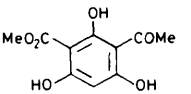
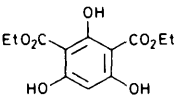
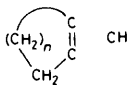
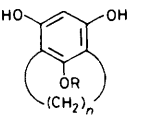
(71)

C. Polyhydroxybenzenes.—In this category the 1,3,5-trihydroxybenzenes have received most attention, probably because of the commercial importance of phloroglucinol and some of its derivatives. Table 8 lists some of the routes published and several of these would appear attractive when compared to conventional routes *via* T.N.T.; the preparation of the bicycle (entry 9) particularly would not be trivial by conventional routes.

Table 8 *Synthesis of trihydroxybenzenes*

Entry	*Precursors*	*Product*	*Yield %*	*Ref.*
1			40	124
2			—	125
3			—	126
4			—	127

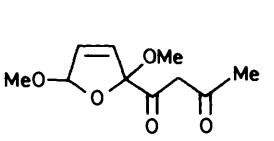
[123] A. J. Bartlett, J. S. E. Holker, E. O'Brien, and T. J. Simpson, *J. Chem. Soc., Perkin Trans. 1*, 1983, 667.
[124] T. M. Harris, M. P. Wachter, G. A. Wiseman, *J. Chem. Soc., Chem. Commun.*, 1969, 177.
[125] Patent, Neth. Appl., 76 09529; *Chem. Abstr.*, **89**, 23951.
[126] G. Waudan, Patent, Ger. Offen, 270 5874.
[127] T. Komninos, *Bull. Soc. Chim. Fr.*, 1918, **23**, 449.

Entry	*Precursors*	*Product*	*Yield %*	*Ref.*
5	$CH_2(CO_2Et)_2$		—	128
6	$EtCH_2COCl$		—	129
7	 $Mg(OMe)_2$		—	130
8	$CH_2(CO_2Et)_2$		25	131
9	 $CH_2(COCl)_2$		18—70	132

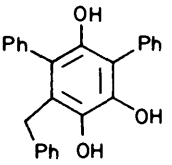
2-Ethylfurancarboxylic ester provides a route *via* (72) to 3-acetyl-1,2,4-trihydroxybenzene (40%), involving several steps;[133] however, 1,2,4-trihydroxybenzene (73) is obtained directly upon reaction of 1,1′-diphenylacetone with 3-phenylcyclobutendione under mild conditions in fairly good yield.[134]

1,2,3-Trihydroxybenzenes figure in several natural products, *e.g.* gallic acid, pyrogallol. Gallic acid (74, R = CO_2H) and pyrogallol (74, R = H) can both be synthesized from ketal (75) and diester (76, R = CO_2H) or (76, R = H), respectively.[135] The yield is fairly good (65%) in both cases. Pyrogallol derivatives can also be prepared by hydrolysis of 2,2;6,6′-tetrahalogenocyclohexanones although the yield is rather poor (20%).[136] Nevertheless, this does provide a convenient synthesis of some potentially highly substituted systems. Finally the tetra-acetylbenzene (77) is prepared from the cyclohexenones (78).[137]

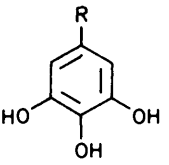
[128] A. Baeyer, *Chem. Ber.*, 1885, **18**, 3454.
[129] A. Combes, *Bull. Soc. Chim.*, 1894, **11**, 710.
[130] T. M. Harris and C. M. Harris, *Tetrahedron*, 1977, **33**, 2159.
[131] H. Leuchs and A. Geserick, *Chem. Ber.*, 1908, **41**, 4171.
[132] F. Effenberger, K.-H. Schonwalder, and J. J. Stezowski, *Angew. Chem., Int. Ed. Engl.*, 1982, **21**, 871.
[133] W. R. Boehme, Patent, U.S. 2 907 794; *Chem. Abstr.*, 1961, **55**, 463.
[134] W. Ried and W. Kunkel, *Justus Liebigs Ann. Chem.*, 1968, **717**, 54.
[135] M. T. Shipchandler, C. A. Peters, and C. D. Hurd, *J. Chem. Soc., Perkin Trans. 1*, 1975, 1400.
[136] Patent, G.B. 1 574 713.
[137] T. Posternak and J. Deshusses, *Helv. Chim. Acta*, 1961, **44**, 2088.



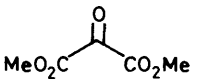
(72)



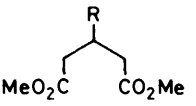
(73)



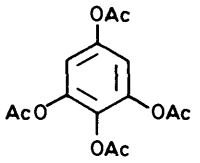
(74)



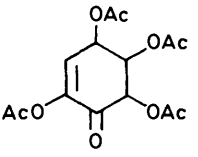
(75)



(76)



(77)



(78)

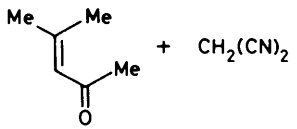
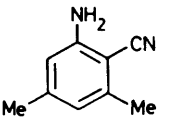
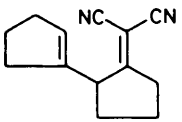
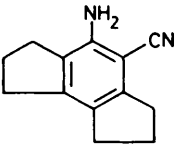
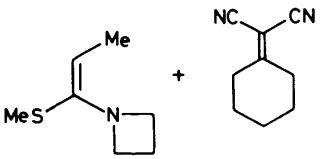
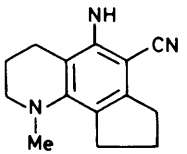
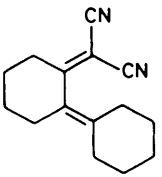
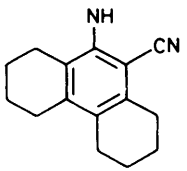
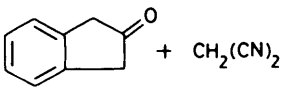
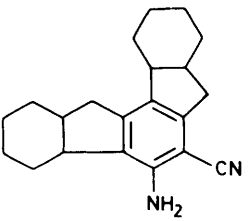
4 Anilines

The synthesis of some anilines has already been discussed in the previous section under the guise of aminophenols. However, the application of ring synthesis methods to anilines is not restricted solely to aminophenols since a wide variety of substituted anilines can be obtained easily from acyclic precursors. In comparison, the amino-group is usually introduced by nitration of the aromatic ring, followed by reduction in the ring functionalization approach, and because this method is such an efficient way of producing anilines, ring synthesis methods can be considered as viable alternatives in only a few cases. One such case is to be found in the preparation of 2-cyanoanilines which probably best illustrates the usefulness of the ring synthesis method. Starting from readily obtained acyclic compounds various highly functionalized cyanoanilines are accessible in quite short synthetic sequences in contrast to the lengthy and tedious routes sometimes found in conventional methods.

Scheme 3 illustrates the strategy *via* the cyclization of ylidene malononitriles, already the subject of a major review.[138] Type I cyclization reactions are carried out under strongly acidic conditions and several examples are shown in Table 9.

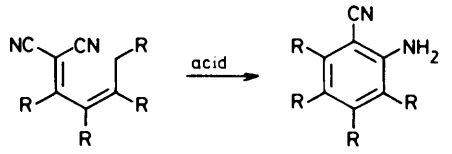
[138] E. Campaigne and S. W. Schnellar, *Synthesis*, 1976, 705.

Table 9 *2-Aminobenzonitriles*

Starting materials	*Product*	*Yield %*	*Ref.*
		55	139
		31	140
		not given	141
		100	142
		54	143

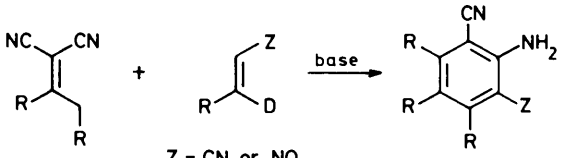
[139] J. Sepiol, J. Mirek, and R. L. Soulen, *Pol. J. Chem.*, 1978, **52**, 1389.
[140] J. Sepiol, B. Kawalek, and J. Mirek, *Synthesis*, 1977, 701.
[141] R. Gompper, W. Elser, and H. J. Muller, *Angew. Chem., Int. Ed. Engl.*, 1967, **6**, 453.
[142] H. Jager, *Chem. Ber.*, 1962, **95**, 242.
[143] H. Junek, O. Wolfbeis, and G. Zacharias, *Monatsh. Chem.*, 1975, **106**, 1207.

Type I



(or bond isomer)

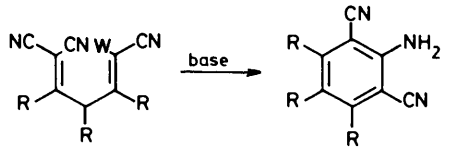
Type II



Z = CN or NO_2

D = Donor group

Type III



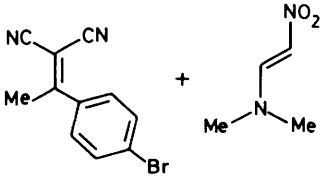
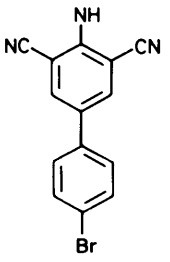
W = CN, CO_2R

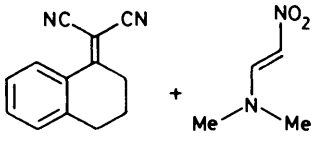
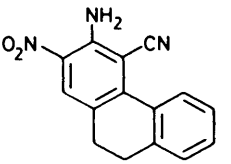
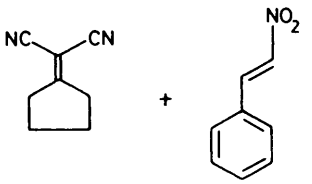
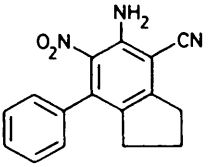
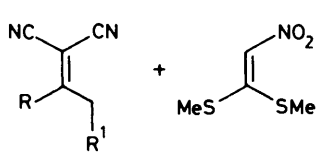
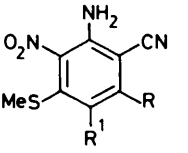
Scheme 3

In contrast, Type II cyclizations are carried out under basic conditions and where nitroalkenes (Z = NO_2) are used 2-cyano-6-nitroanilines result (see Table 10). If the nitroalkene carries a β-amino- or a β-thio-substituent then the group at the β-position is eliminated during the cyclization reaction, whereas an aryl group is retained, as might be expected.

Type II and III cyclizations offer very effective routes into 2,6-dicyanoanilines as

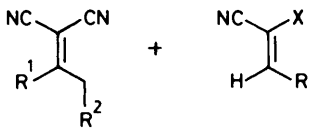
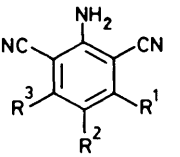
Table 10 *6-Nitro-2-aminobenzonitriles*

Starting materials	*Product*	*Yield %*	*Ref.*
		40	144

Starting materials	*Product*	*Yield %*	*Ref.*
		45	144
		36	145
		76—90	146

can be seen from Table 11, and as Table 11 shows, the ylidenemalonitriles required for Type III cyclization can also be generated *in situ* from 1,3-diketones and their N and S analogues. These routes are particularly important in view of the laborious, multi-step syntheses which are necessary with conventional methods.

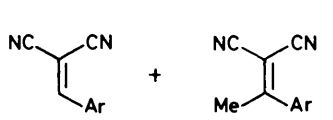
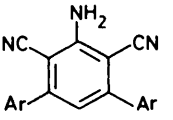
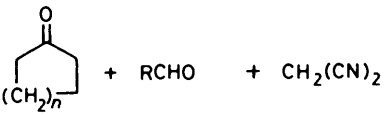
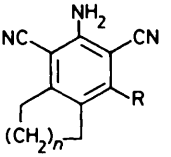
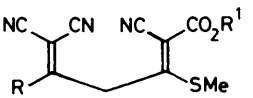
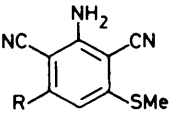
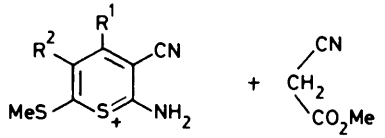
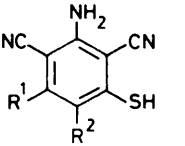
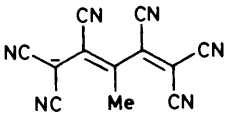
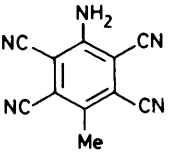
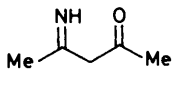
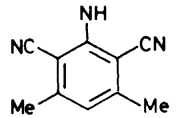
Table 11 *2-Amino-1,3-phthalodinitriles*

Starting materials	*Product*	*Yield %*	*Ref.*
		60—90	145

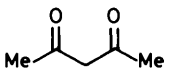
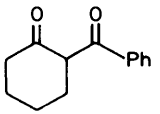
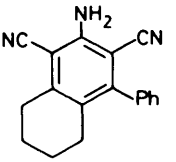
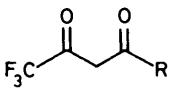
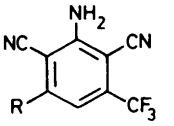
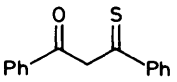
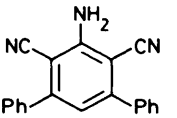
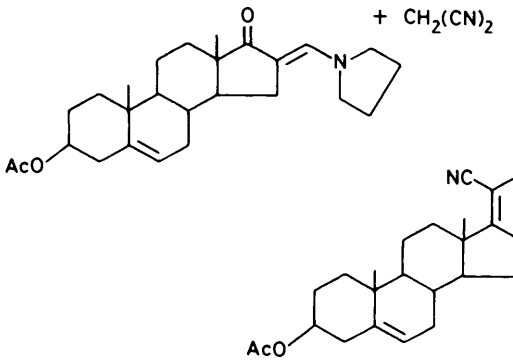
R^1 = Ph, Et; R^2 = H, Me; R^1, R^2 = —$(CH_2)_4$—

R^3 = Ph, Me; X = CN, CO_2Me

[144] T. Severin, B. Bruck, and P. Adhikary, *Chem. Ber.*, 1966, **99**, 3097.
[145] K. Gewald and W. Schill, *J. Prakt. Chem.*, 1971, **313**, 678.
[146] K. Peseke and J. Q. Suarez, *Z. Chem.*, 1981, **21**, 405.

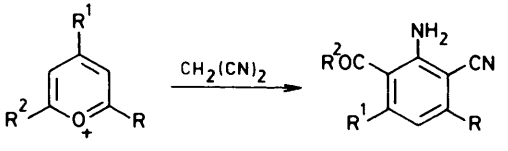
Starting materials	*Product*	*Yield %*	*Ref.*
		75—77	147
Ar = 4-R-C_6H_4—; R = H, Cl, F			
		—	148
n = 1—3 R = Bu^t, indolyl, or $R^1C_6H_4$—			
		72—77	149
R = Ph, 4-$MeOC_6H_4$—			
		83—92	150
R^1, R^2 = Me, Et, $-(CH_2)_4-$			
		55	151
 + $CH_2(CN)_2$		40	152

[147] Y. Abramenko, Y. A. Baskakov, Y. A. Sharanin, N. A. Kiseleva, U. N. Vlasov, Y. G. Putsykin, and V. V. Negrebetskii, *Zh. Vses. Khim. Ova.* 1979, **24**, 409 (*Chem. Abstr.*, 1979, **91**, 193 126).
[148] Y. Abramenko, Y. A. Baskakov, Y. A. Sharanin, A. F. Vasilev, Y. G. Putsykin, and E. B. Nazarova, *J. Org. Chem. USSR*, 1980, **16**, 1870.
[149] K. Peseke, *J. Prakt. Chem.*, 1983, **323**, 499.
[150] K. Gewald and H. Schafer, *Z. Chem.*, 1981, **21**, 183.
[151] H. C. Gardner and J. K. Kochi, *J. Am. Chem. Soc.*, 1976, **98**, 558.
[152] R. Hull, *J. Chem. Soc.*, 1951, 1136.

Starting materials	*Product*	*Yield %*	*Ref.*
	–ditto–	50—55	153
		85	154
		31—75	155
		70	156
		42	157

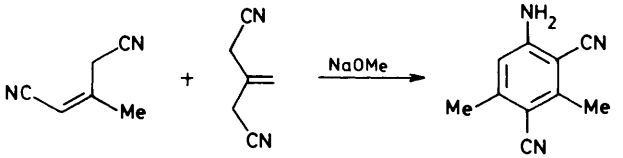
[153] Patent, U.S.S.R. 521, 260, 1974 (*Chem. Abstr.*, **85**, 177041).
[154] Y. A. Sharanin, L. A. Rodionovskaya, V. K. Promonenkov, and A. M. Shestopalov, *Zh. Org. Khim.*, 1983, **19**, 1781.
[155] E. Gudriniece, A. V. Guttsait, S. V. Belyakov, and A. N. Fomin, *Latv. PSR Zinat. Akad. Vestis, Kim. Ser.*, 1983, 245 (*Chem. Abstr.*, 1983, **99**, 53298d).
[156] Y. A. Sharanin and K. Y. Lopatinskaya, *J. Org. Chem. U.S.S.R.*, 1976, **12**, 688.
[157] B. Green, I. S. Khaidem, R. I. Crane, and S. S. Newaz, *Tetrahedron*, 1976, **32**, 2997.

6-Acyl-2-cyanoaniline (79) can also be conveniently synthesized by a Type III cyclization and once again the intermediate ylidenemalononitrile is generated *in situ*, this time from a pyrylium salt and malononitrile.[158,159]



(79)

An excellent though limited method for making a 2,4-dicyanoaniline (80) has been described,[160] and involves the condensation of β-methyleneglutaric acid dinitrile or β-methylglutaconic acid dinitrile in high yield.

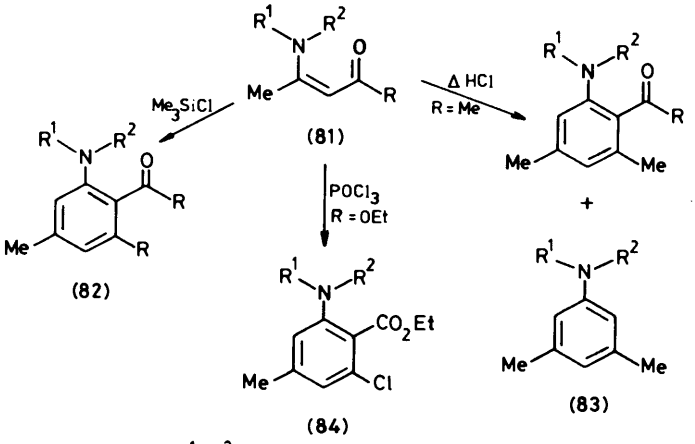


(80)

In all the examples so far described the amino-group is formed by condensation at a nitrile group which inevitably leads to the formation of a primary amine. However, the amino-group in the aniline can originate from an enamino-group; this then allows for the direct synthesis of secondary and tertiary anilines. Self condensation of β-enaminoketones (81) provides a simple though rather unattractive route to 2-aminophenones as described in Scheme 4. If trimethylsilylchloride is used as co-reactant then the yield of phenone (82) is good although pyridines are formed as by-products.[161] If the reaction is catalysed by acid 3,5-xylidenes (83) are also formed.[162] Nevertheless the $POCl_3$ induced dimerization of enaminoesters does provide good yields of the aniline esters (84).[163]

There have been several reports on the use of enamines and enediamines to make *N,N*-dialkylanilines, but they have been generally of limited synthetic utility.[164] However, a recent paper has described a route which appears to offer some potential as a general method for the synthesis 2,6-disubstituted anilines. Thus 1,3-dichloro-1,3-dimethoxypropane condenses with enamines (85) to give the 2,6-disubstituted anilines (86) in moderate yields and would presumably be of wider application.[165]

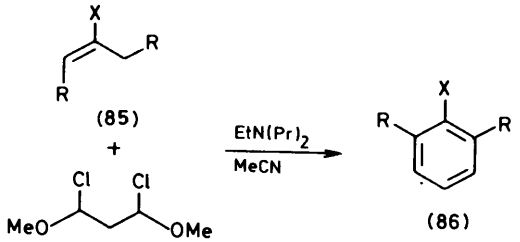
[158] K. Dimroth and G. Neubauer, *Angew. Chem.*, 1957, **69**, 720.
[159] K. Dimroth and G. Neubauer, *Chem. Ber.*, 1959, **92**, 2046.
[160] U.K. Patent, 1 374 954, 1972.
[161] C. Kashima and Y. Yamamoto, *J. Heterocycl. Chem.*, 1980, **17**, 1141.
[162] S. Auricchio, R. Bernardi, A. Ricca, *Tetrahedron Lett.*, 1976, 4831.
[163] R. L. N. Harris, J. L. Huppatz, and J. N. Phillips, *Angew. Chem., Int. Ed. Engl.*, 1976, **15**, 498.
[164] P. N. Hickmott and C. T. Yoxall, *J. Chem. Soc. C*, 1971, 1829.
[165] F. Camps, C. Jaime, and J. Molas, *Tetrahedron Lett.*, 1981, **22**, 2487.



R^1, R^2 = Me, Et, $-(CH_2)_n-$ n = 4 or 5

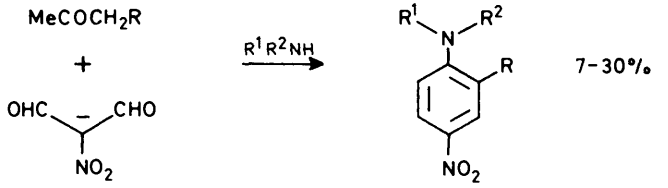
Yields 78–89%

Scheme 4

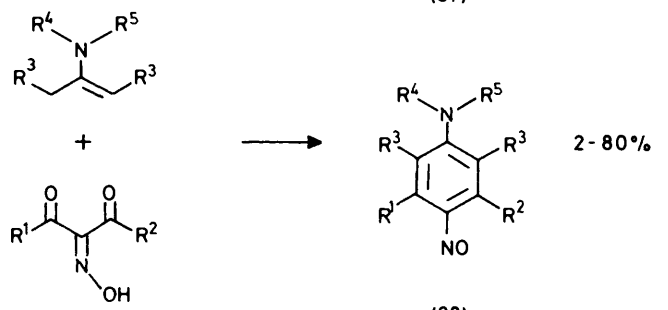


X	R	*Yield* %
	Me	38
	Ph	52
	Ph	54

The dichlorodimethoxypropane just described is a synthetic equivalent of malondialdehyde and it is therefore not surprising to see that nitromalondialdehyde reacts with enamines, generated *in situ*, to give substituted 4-nitroanilines (87).[166] Similarly enamines react with oximino-diketones to give the corresponding 4-nitroso-anilines (88) in poor to excellent yield.[167] These latter two reactions are simple extensions of the phenol syntheses, described in Section 3, *e.g.* see Hill and Prelog syntheses, and so many of the comments recorded there apply equally to these reactions.



(87)



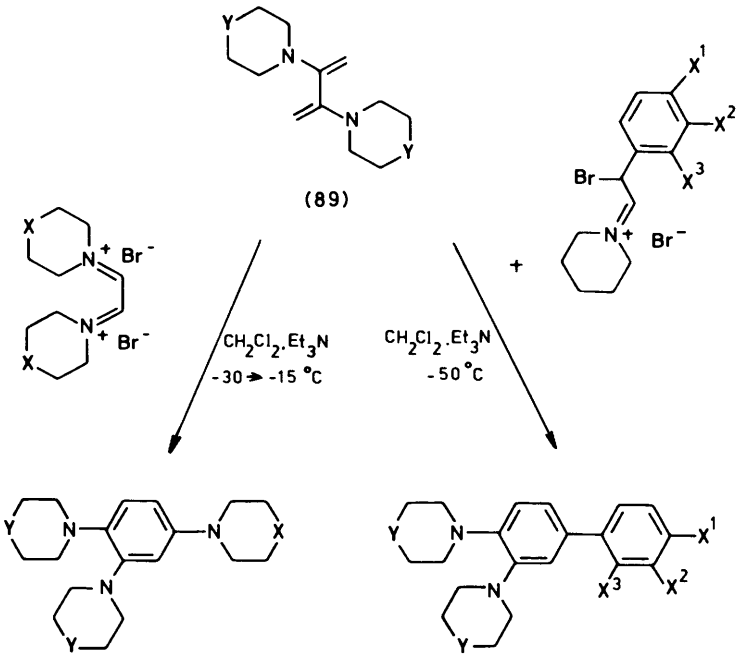
(88)

The double enamines (89) have been the focus of some fairly recent attention and provide access to either 1,2,4-triaminobenzenes (90) or 1,2-diaminobiphenyls (91) depending upon conditions and co-reactants. Although the yields are not high the substitution patterns are not common.[168,169]

In the preparation of (90) and (91) highly reactive imminium salts were used and this approach is further exemplified in the preparation of 1,3,5-tri-(*N*,*N*-diethylamino)benzene in quantitative yield from the vinamidinium salt (91).[170] Unfortunately, the reactions would appear to be of rather limited scope.

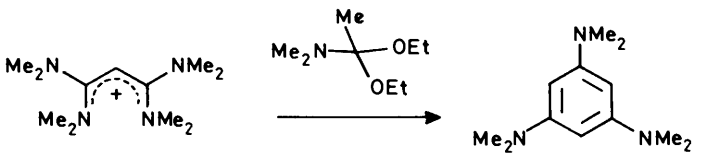
The similarity between several of the routes to anilines and those to phenols (Section 1) has already been highlighted. Continuing on this theme, heterocyclic compounds such as pyrylium and pyridinium salts have both been shown to provide routes into phenols and by use of the appropriate co-reactants will also

[166] R. A. Sagitullin, S. P. Gromov, and A. N. Kost, *J. Org. Chem. USSR*, 1978, **14**, 1554.
[167] E. Yu. Belyaev, G. A. Suboch, and A. V. El'tsov, *J. Org. Chem. USSR*, 1978, **14**, 1407.
[168] S. Baroni, E. Rivera, R. Stradi, and M. L. Saccarello, *Tetrahedron Lett.*, 1980, **21**, 889.
[169] G. Crispi, P. Giacconi, E. Rossi, and R. Stradi, *Synthesis*, 1982, 787.
[170] R. Gompper and U. Heinemann, *Angew. Chem., Int. Ed. Engl.*, 1981, **20**, 297.



X	Y	*Yield* %	X^1	X^2	X^3	Y	*Yield* % (91)
O	O	50	H	H	H	O	25
CH_2	O	55	H	H	H	CH_2	25
NMe	O	70	OMe	H	H	O	47
O	CH_2	58	H	NO_2	H	O	15
CH_2	CH_2	46	F	H	H	O	25
NMe	CH_2	62	OMe	OMe	H	O	25

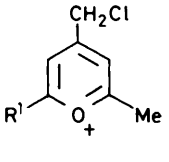
Scheme 5



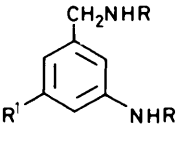
yield anilines. For example the pyrylium salt (93) gives *m*-aminomethyl anilines (91)[171] and alkylpyridinium salts rearrange to anilines when treated with amine

[171] U.S.S.R. Patent 659 562, 1979 (*Chem. Abstr.*, 1979, **91**, 93122).

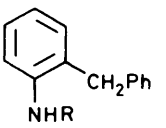
sulphates at elevated temperature.[172–4] A potentially useful reaction of this type is the preparation of 2-aminodiphenylamines (95) from the corresponding amine sulphate and alkylpyridinium salt (96).[173]



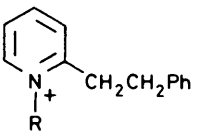
(93)



(94)

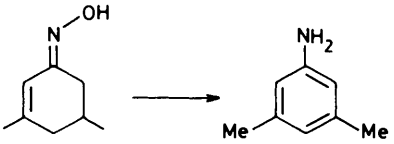


(95)



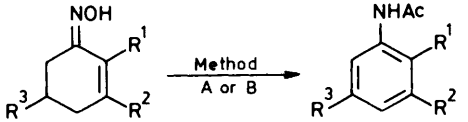
(96)

Aromatization reactions have been largely ignored in this review despite extensive literature precedent. However, the Semmler–Wolf aromatization of cyclohexenone oximes is worthy of mention. The Semmler–Wolf reaction was first published last century and was effected by heating cyclohexenone oximes with strong acids, *e.g.* equation 3.[175] Since then a variety of reagents have been found,



(3)

Table 12



A = *p*-TosOH/CH_2=C=O/MeCN, 70—80 °C
B = *p*-TosOH/CH_2=C(OEt)OAc/MeCN, 80 °C

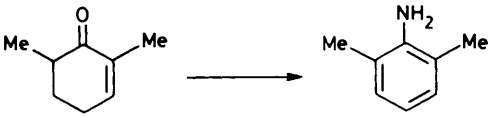
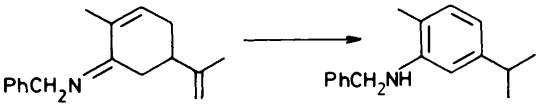
R^1	R^2	R^3	*Yield* %	*Method*
H	Ph	H	85	A
H	H	H	50	A
H	Me	H	61	A
H	Me	Me	61	A
H	Me	Me	62	B
H	OMe	Me	76	B
H	Cl	Ph	67	B
$-CH_2-CH(OMe)-O-$		H	40	B
H	SCN	H	50	B

[172] T. V. Stupnikova, A. I. Sedyink, V. N. Kalafat, R. S. Segitullin, and V. P. Marshtup, *Khim. Geterotsikl Soedin.*, 1981, 508.
[173] A. N. Kost, L. G. Yudin, A. N. Rumyanstev, and R. S. Sagitullin, *Khim. Geterotsikl. Soedin.*, 1982, 270.
[174] A. N. Kost, L. G. Yudin, A. N. Rumyanstev, and R. S. Sagitullin, *Khim. Geterotsikl. Soedin.*, 1983, 63.
[175] W. Semmler, *Berichte*, 1892, **25**, 3352.

such as acetic anhydride, polyphosphoric acid, and mixed acid, which will effect the reaction and various anilines are now accessible by this route.[176] More recently a mild and synthetically useful reaction has been published (see Table 12) and involves the use of toluenesulphonic acid with ketene, or with a synthetic equivalent of ketene, at 70—80 °C with acetonitrile as solvent. The yields are fairly good and a number of differently substituted anilines are readily accessible.[177]

Dehydrogenations have also been used extensively to generate anilines, usually from imines, and Table 13 illustrates some of these reactions. Particularly noteworthy is the preparation of 2,6-dimethylaniline, a commercially useful compound used in the pharmaceutical industry.[179]

Table 13

	Conditions	*Ref.*
	Pd/Al_2O_3 210 °C	178
	$Pd/C{\cdot}NH_3$ 290 °C	179
	$RhCl_3/K_2CO_3$ 100 °C	180

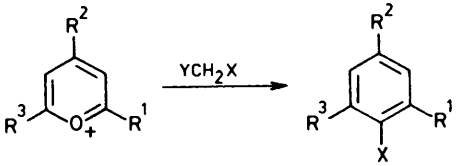
5 Benzenes containing at least one Acceptor Group

The reaction of pyrylium salts with an active methylene compound is a general route into benzenes having only one electron-withdrawing group and bearing alkyl or aryl groups in the 2, 4, and 6 positions.[181] The electron-withdrawing group can be chosen from nitro, cyano, ester, and ketone groups and, as can be seen from

[176] Y. Tamura, Y. Yoshimoto, K. Sakai, and Y. Kita, *Synthesis*, 1980, 483, and references therein.
[177] Y. Tamura, Y. Yoshimoto, K. Sakai, J. Haruta, and Y. Kita, *Synthesis*, 1980, 887.
[178] Eur. Pat. Appl. EP 51805, 1982 (*Chem. Abstr.*, 1982, **97**, 162556).
[179] Brit. Pat. 1 565 849, 1975 (*Chem. Abstr.*, 1981, **94**, 30328).
[180] P. A. Grieco and N. Marinovic, *Tetrahedron Lett.*, 1978, 2545.
[181] K. Dimroth and K. H. Wolf, 'Newer Methods of Organic Chemistry', Vol. 3, ed. W. Foerst, Academic Press, New York, 1964, p. 357.

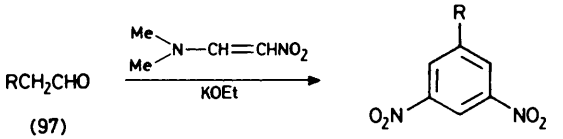
Table 14, the reaction is quite versatile. Those entries shown in Table 14 are illustrative examples and many more are to be found in the general literature.[182–184]

Table 14



R^1	R^2	R^3	X	Y	*Yield* %	*Ref.*
Me	Me	Me	NO_2	H	72	182*a*
Me	Ph	Ph	NO_2	H	48	182*a*
Ph	Ph	Ph	NO_2	H	85	182*a*
$C_6H_4Br(4)$	Ph	Ph	NO_2	H	64	182*a*
$C_6H_4OMe(4)$	$C_6H_4OMe(4)$	$C_6H_4OMe(4)$	NO_2	H	60	182*a*
Me	SMe	Me	NO_2	H	42	183
Ph	Ph	Ph	CO_2Et	COMe	32	182*b*
Ph	Ph	Ph	COMe	COMe	70	182*b*
Ph	Ph	Ph	CN	CO_2Et	81	182*b*
Me	OMe	OMe	CO_2Et	$PO(OMe)_2$	65	184

Early work by Hill and his co-workers showed that the sodium salt of nitromalondialdehyde could be trimerized to 1,3,5-trinitrobenzene but this is of no practical significance.[185] More recently, two routes to 1,3-dinitrobenzenes have been devised which offer greater practical utility; both used nitroacetylene synthons. The first of these involves a stepwise reaction of β-*N*,*N*-dimethylaminonitroethylene with an aldehyde (97) to give low yields of the 1,3-dinitrobenzenes (98) carrying alkyl (or aryl) substituents at the 5-position.[186]

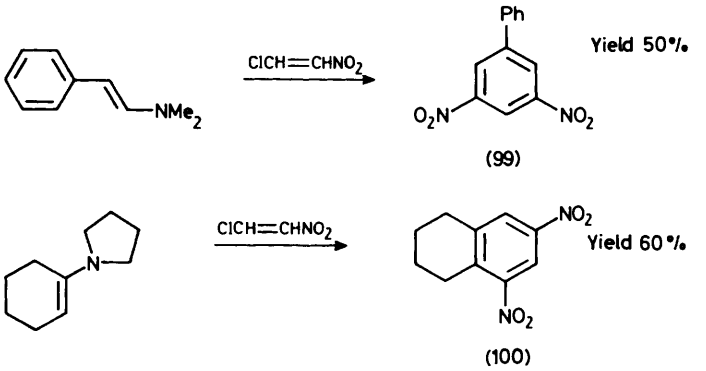


(98)

R	*Yield* %
H	20
Me	24
Ph	40

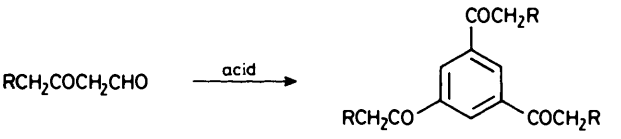
[182] (*a*) K. Dimroth, G. Brauniger, and G. Neubauer, *Chem. Ber.*, 1957, **90**, 1634; (*b*) K. Dimroth and G. Brauniger, *Chem. Ber.*, 1959, **92**, 2042.
[183] M. Ohta and H. Kato, *Bull. Chem. Soc. Jpn.*, 1959, **32**, 707.
[184] D. A. Griffin and J. Staunton, *J. Chem. Soc., Chem. Commun.*, 1971, 675.
[185] H. B. Hill and J. Torrey, *Berichte*, 1895, **28**, 2597.
[186] T. Severin, P. Adhikary, E. Dehmel, and I. Eberhard, *Chem. Ber.*, 1971, **104**, 2856.

The second method uses β-chloronitrothylene in a condensation reaction with enamines to give aryl-substituted 1,3-dinitrobenzenes (99) or annelated derivatives (100).[187] On the limited evidence the yields are better than in the previous example and further exploration would seem justified.



A related reaction is the thermal cyclization of 6-nitrosubstituted 1-dimethylaminohexatrienes.[188]

β-Ketoaldehydes will also trimerize (*cf.* 2-nitromalondialdehyde) under acid conditions to provide a useful route to 1,3,5-triketobenzenes (101); experimental conditions have been described in *Organic Syntheses*,[190] although it would appear that enamines give higher yields when used.[191]



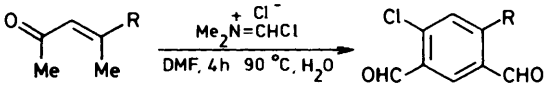
(101)

	R	*Yield* %	*Ref.*
	H	46	189
	Me	27	190
	$PhCH_2$	29	190
(*via* enamine)	H	94	191

On the other hand aromatic aldehydes have been prepared by an interesting route which involves the use of chloromethyleneiminium salts.[192] Thus, with vinylketones (102) the products are 6-chloro-1,3-benzenedicarboxaldehydes (103);

[187] H. G. Viehe and R. Verbruggen, *Chimia*, 1975, 352.
[188] C. Jutz and R. M. Wagner, *Angew. Chem., Int. Edn. Engl.*, 1972, **11**, 315.
[189] *Organic Syntheses*, Coll. Vol. III, John Wiley, 1955, p. 829.
[190] T. M. Harris, S. Boatman, and C. R. Hauser, *J. Am. Chem. Soc.*, 1963, **85**, 3273.
[191] N. K. Kochetkov, *Izv. Akad. Nauk SSSR*, 1953, 991 (*Chem. Abstr.*, 1955, **49**, 2308).
[192] A. Holy and Z. Arnold, *Collect. Czech. Chem. Commun.*, 1965, **30**, 53.

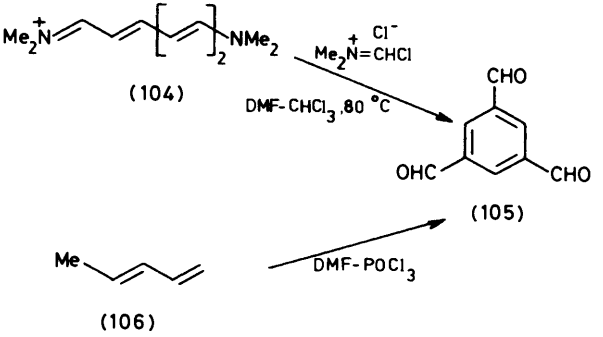
however, the yields are only moderate although the reagents are cheap and the conditions relatively mild. In a similar fashion acetylacetone was found to give 2,4-dichlorobenzaldehyde in 84% yield. This interesting reaction has not been extended to substituted 1,3-diketones.



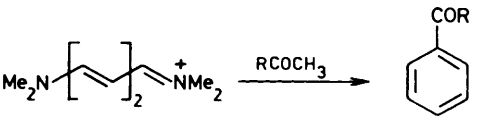
(102) (103)

R = H, Me, NMe_2,
Yields 33–48%

Polymethines (104) will also react with an iminium salt to give the tricarboxaldehyde (105), and Russian workers have claimed that piperylene (106) can be converted directly into (105) under Vilsmeier–Haak conditions.[193] The yields from these routes are 40% and 28% respectively.



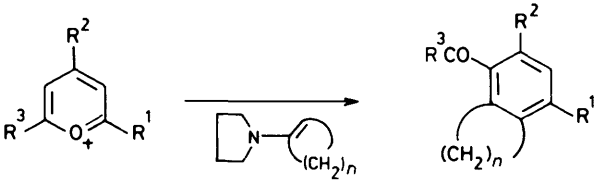
In a variant of this reaction it has been shown that condensation of the pentamethylene iminium salt (107) with methyl ketones will give the phenones (108) in excellent yields.[194] This reaction will however be of little practical importance until the effect of substituents on the chain has been studied.



(107) (108)

[193] T. I. Lonshchakova, B. I. Buzykin, A. G. Liakumovich, and V. S. Tsivunin, *J. Org. Chem. USSR*, 1978, **14**, 550.
[194] C. Jutz, R. M. Wagner, A. Kratz, and H. G. Lobering, *Ann.*, 1975, 874.

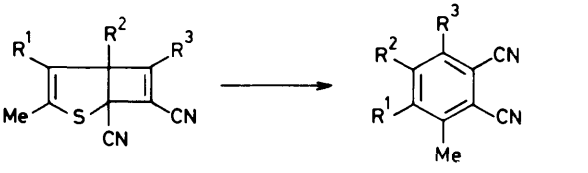
A related electrocyclic cyclization of a 6-hydroxyhexatrienecarboxaldehyde to benzaldehyde suffers from the same limitations.[195] Of greater utility, for annelated products, is the condensation rearrangement reaction between (109) and enamines to give (110).[196]



(109) (110)

R^1	R^2	R^3	*n*	*Yield* %
Ph	Ph	Ph	3	64.5
Me	Ph	Ph	3	17
Ph	Ph	Ph	4	56
Ph	Ph	Ph	6	63.2
Ph	Ph	Ph	10	19.2

Condensation routes to benzene carboxylic acids or esters without any other functional groups on the ring are very few in number. They are, however, readily made by Diels–Alder cycloaddition reaction; as stated earlier this is outside the scope of this report. In general those reactions which give simple monocarboxylic acids are, apart from those made *via* pyrylium salts described earlier, of little import to the synthetic chemist. Exceptions might be those involving annelated benzene rings.[197] The same comments can be made about routes to simple benzo- or phthalo-nitriles. There are however several useful routes to mono-, di-, and tri-nitriles in the naphthalene series.[198–200] An interesting recent example involves the extrusion of sulphur from the 2-thiabicyclo[3.2.0]hepta-3,6-diones (111) to give the



(111) (112)

R^1, R^2, and R^3 = H, Me, or CMe_3

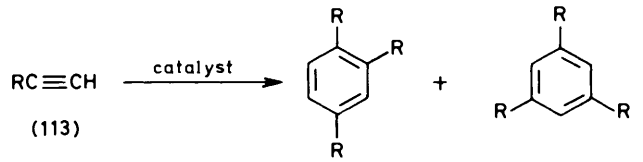
[195] H. Althoft, B. Bornowski, and S. Dahne, *J. Prakt. Chem.*, 1977, **319**, 890.
[196] G. Markl and H. Baier, *Tetrahedron Lett.*, 1968, 4379.
[197] J. B. Dickenson and W. Reusch, *Synth. Commun.*, 1983, **13**, 303.
[198] C. Jutz and H. G. Peuker, *Synthesis*, 1975, 431.
[199] H. Moureu, P. Chovin, and G. Rivoal, *Bull. Soc. Chim. Fr.*, 1946, 106.
[200] L. Heiss, E. F. Paulus, and H. Rehling, *Ann.*, 1980, 1583.

substituted phthalonitriles (112) in 44—52% yield.[201] The starting materials are fairly readily obtainable by the thermal rearrangement of the (2 + 2) cycloaddition products from the corresponding thiophenes and 2-butynedinitrile.

6 Alkyl- and Aryl-substituted Benzenes

An important method for synthesizing polyalkyl- or polyaryl-benzenes from acyclic precursors is the cyclotrimerization of alkynes. The reaction was first described by Reffe in 1948,[202] and requires the intervention of a transition-metal catalyst. The most common catalysts are metal carbonyl complexes of Ni, Co, and Cr or Ziegler–Nattar catalysts of the type R_3Al–$TiCl_4$. There have been many good reviews on this topic which are essential reading for anyone intending to carry out work in this area.[203–207] These reviews also cover the introduction of alkene, alkyne, ether, carboxylic acid (esters), amino, chloro, cyano, and silyl groups into benzene *via* the appropriately substituted alkyne, a route ignored in previous sections of this review. The balance will therefore be redressed in this section.

There is little doubt that this type of reaction is of practical value in the synthesis of tri- to hexa-substituted alkyl- or aryl-benzenes. However, a disadvantage of the method when using monosubstituted alkynes is that the products are often mixtures of the two possible isomers, the 1,2,4- or 1,3,5-trisubstituted benzenes. Similarly the co-oligomerization of different alkynes often gives a gross mixture of

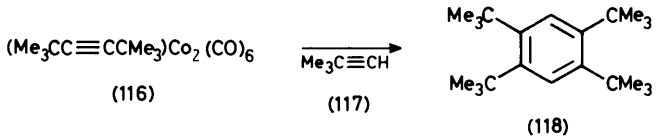


(113) (114) (115)

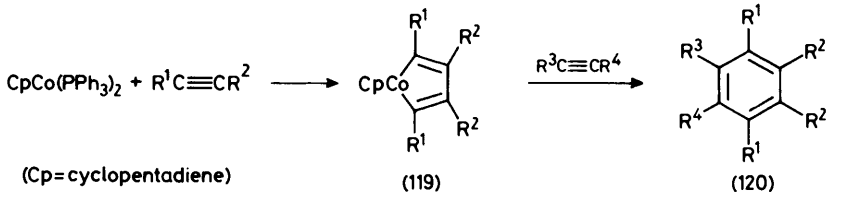
all the possible products with little or no selectivity.[203,207] An elegant solution to this problem is to preform an alkyne–metal complex and then add a second different alkyne to give the substituted benzene. This is exemplified by the formation of 1,2,4,5-tetra-t-butylbenzene (118), where, although the overall yield is only 21%, its synthesis by a more conventional route would be difficult.[208]

A very interesting development on this theme is the so-called 'cobalt system'.

[201] R. H. Hall, H. J. den Hertog, D. N. Reinhoudt, S. Harkema, G. J. van Hummel, and J. W. H. M. Uiterwijk, *J. Org. Chem.*, 1982, **47**, 977.
[202] W. H. Reppe, O. Schlichting, K. Klager, and T. Toepel, *Ann.*, 1948, **560**, 1.
[203] C. W. Bird, 'Transition Metal Intermediates in Organic Synthesis', Logos Press, London, 1967, Chapter 1.
[204] L. D. Yur'eva, *Russ. Chem. Rev.*, 1974, **43**, 48.
[205] K. P. C. Vollhardt, *Acc. Chem. Res.*, 1977, **10**, 1.
[206] K. M. Nicholas, M. O. Nestle, and D. Seyferth, in Transition Metal Organometallics in Organic Synthesis', Vol. 2, ed. H. Alper, Academic Press, New York, 1978, p. 26.
[207] C. Hoogzand and W. Hubel, 'Organic Synthesis *via* Metal Carbonyls', Vol. 1, ed. I. Wender and P. Pino, Wiley, New York, 1968, p. 343.
[208] U. Kruerke, C. Hoogzand, and W. Hubel, *Chem. Ber.*, 1961, **94**, 2817.

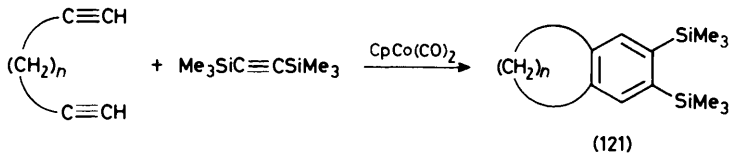


This involves the reaction of $CpCo(PPh_3)_2$, with two or three different alkynes in a stepwise manner *via* a cobaltocycle (119) to the benzene (120), as outlined below.[209]



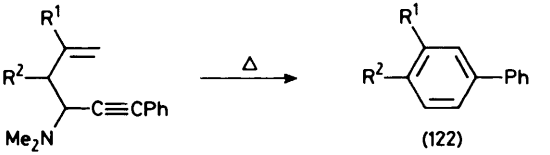
This method offers a much higher degree of control than previous methods and is of value in producing highly substituted benzenes. A major disadvantage of this method is that it requires stoicheiometric quantities of the complex. However, a catalytic cobalt system has been described which makes use of a sterically hindered acetylene, *e.g.* bistrimethylsilylacetylene, that will add to other acetylenes without undergoing trimerization.[205]

A procedure can then be adopted where bistrimethylsilylacetylene is used both as a reactant and as a part of a recyclable solvent system, together with catalytic quantities of the commercially available $CpCo(CO)_2$. This method is particularly useful in the production of annelated benzenes (121). Recent developments in the chemistry of the trisilylmethyl groups should allow the introduction of further functionality into the derived products.[210]



A miscellany of methods for the formation of polyalkyl- or polyaryl-benzenes by the condensation of carbonyl compounds have been described over the years but very few of these have any practical significance. A notable exception is the conversion of acetone into mesitylene, full details of which are given in *Organic Syntheses*.[211] A particularly interesting and useful objective in this area is a method for producing unsymmetrical poly-aryl compounds and this is shown below.

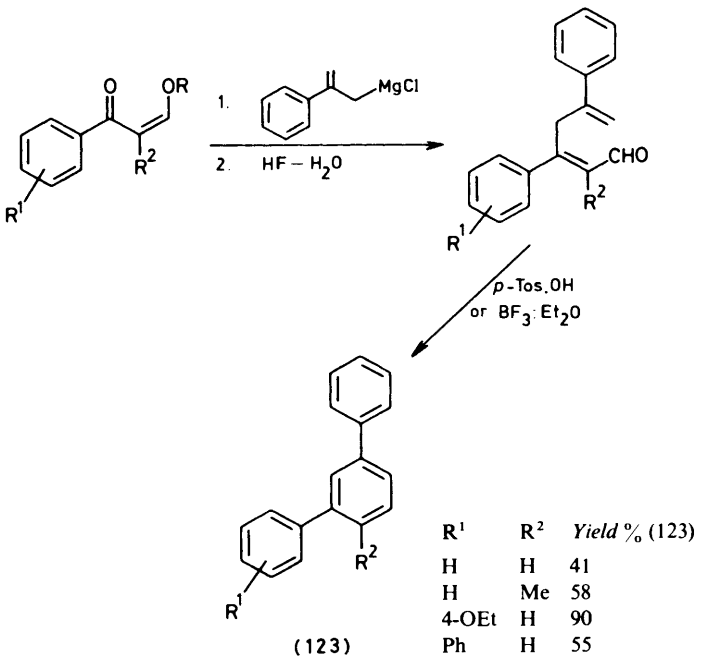
[209] T. Wakatsuki, T. Kuramitsu, and H. Yamazaki, *Tetrahedron Lett.*, 1974, 4549.
[210] T. H. Chan and I. Fleming, *Synthesis*, 1979, 761.
[211] *Organic Syntheses*, Coll. Vol. 1, John Wiley, May 1961, p. 341.



(122)

R^1	R^2	*Temp*/°C	*Time*	*Yield* % (122)
H	Ph	140	1 hour	70
H	Me	200	3 days	60
H	Me	140	7 days	58
Ph	H	140	3 days	95
Me	H	200	12 hours	95

Although good to excellent yields of (122) can be obtained the process tends to be slow and unsuitable for thermally labile groups.[212] A good route has recently been proposed using Grignard reagents and is illustrated in Scheme 6.[213–215] The stepwise process is especially useful for unsymmetrical *m*-terphenyls.[215]



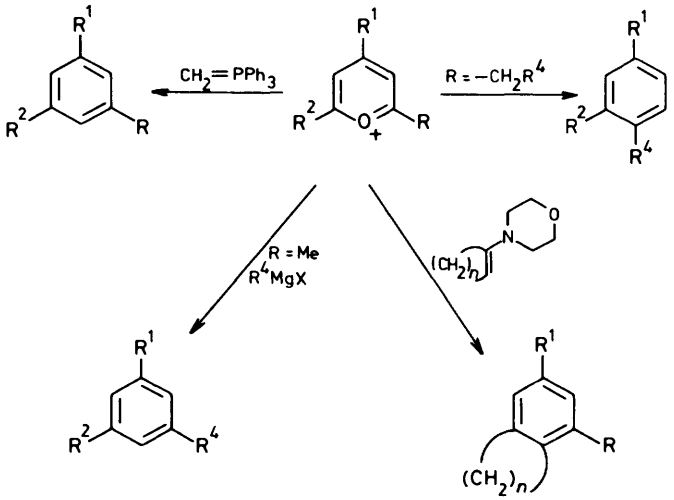
(123)

R^1	R^2	*Yield* % (123)
H	H	41
H	Me	58
4-OEt	H	90
Ph	H	55

Scheme 6

[212] R. W. Jemison, T. Laird, and W. D. Ollis, *J. Chem. Soc., Chem. Commun.*, 1972, 556.
[213] M. A. Tius, *Tetrahedron Lett.*, 1981, **22**, 3335.
[214] M. A. Tius and S. Ali, *J. Org. Chem.*, 1982, **47**, 3163.
[215] M. A. Tius and S. Savariar, *Synthesis*, 1983, 467.

Pyrylium salts, as described elsewhere in this review, provide an entry point into polysubstituted aromatic compounds.[181] The routes which are applicable to alkyl- or aryl-benzenes are shown in Scheme 7.

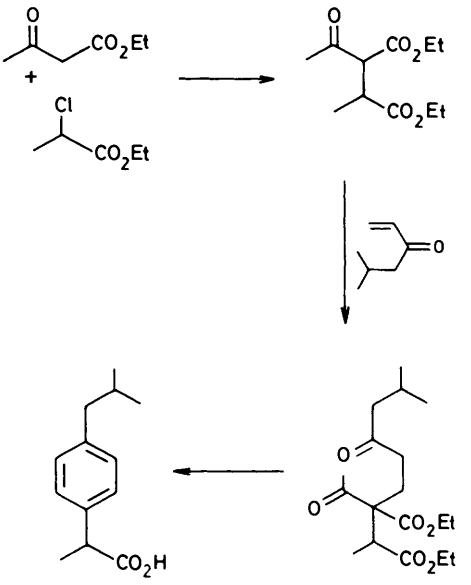


Scheme 7

The original substitution pattern can be maintained in the derived 1,3,5-trisubstituted benzene by reaction with Wittig reagents, or a new 5-substituent can be introduced by reacting a Grignard reagent with a 2-methylpyrylium salt. By suitable choice of substituents the pyrylium salt can be ring opened and then closed into a 1,3,4-pattern. Reaction with enamines provides a route into annelated benzenes, but in this case there is a competing reaction which gives the aryl ketone. In general the yields from the reactions of pyrylium salts are only moderate and the synthesis of unsymmetrical pyrylium compounds is often not easy. In spite of these drawbacks this method is worth considering especially as a route to 1,3,5-triarylbenzenes.

The importance of phenylalkanoic acids as intermediates in the manufacture of drugs has lead to a great deal of synthetic activity in the area.[216–218] An important target of this work has been the drug Ibuprofen (124). The Upjohn Company have devised an elegant route to this compound from readily available aliphatic starting materials.[218]

[216] Patent, U.S. 4 189 596, 1980 (*Chem. Abstr.*, 1980, **93**, 7862).
[217] Patent, U.S. 4 154 962 (*Chem. Abstr.*, 1976, **85**, 142842).
[218] Patent, Ger. 2 806 424, 1978 (*Chem. Abstr.*, 1978, **89**, 214917).



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