One-step synthesis of polysubstituted benzene derivatives by multi-component cyclization of α-bromoacetate, malononitrile and aromatic aldehydes†

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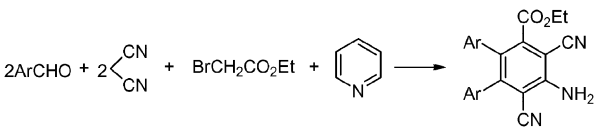
Polysubstituted benzene derivatives with an unprecedented substitution pattern are produced in a novel one-pot multi-component cyclization reaction from pyridine, ethyl α-bromoacetate, malononitrile and aromatic aldehyde in refluxing acetonitrile.

Multicomponent reactions are one-pot processes in which several easily accessible components react to form a single product. They offer significant advantages over conventional linear-type syntheses due to their flexible, convergent and atom efficient nature and have become an important area of research in organic, medicinal and combinatorial chemistry.[1–3] According to current synthetic requirements, effective and environmentally benign multicomponent procedures are particularly welcome.[4] Malononitrile is an exceptionally versatile compound in this context and is therefore used extensively as a reactant or reaction intermediate. It exhibits unique reactivity since the strongly electron-withdrawing cyano groups activate the methylene group (pK_a = 11.2), their polar multiple bond is suitable for nucleophilic addition and is also a good leaving group for substitution.[5] The methylene group and either one or both cyano groups can take part in condensation reactions to give a variety of addition products and heterocyclic compounds.[6] This exceptional behavior makes malononitrile an important candidate for the design of new practical multicomponent reaction procedures in research and in medicinal, industrial and agricultural chemistry. In fact there are a lot of multicomponent reaction procedures with malononitrile to prepare carbocyclic and heterocyclic compounds.[6–8] Herein we wish to report our investigation of a new multicomponent reaction which involves malononitrile, aromatic aldehyde, pyridine and ethyl α-bromoacetate for the synthesis of polysubstituted benzene compounds (Scheme 1).‡

When a mixture of malononitrile, benzaldehyde, ethyl α-bromoacetate and an excess of pyridine was heated in acetonitrile for several hours, the unexpected polysubstituted benzene derivative **1a** (ethyl 3-amino-2,4-dicyano-5,6-diphenylbenzoate) was isolated in 31% yield after workup. Similarly, various aromatic aldehydes reacted well under the same conditions to give the corresponding polysubstituted benzene derivatives **1b–1h** in moderate yields. Benzaldehydes with substituents of moderate electronic influence such as bromo, chloro, methyl and *tert*-butyl afforded the desired products (Table 1). In contrast, benzaldehydes with stronger electron-donating groups such as methoxy, hydroxyl and dimethylamino or with stronger electron-withdrawing groups such as the nitro group did not give the polysubstituted benzenes, affording only gummy materials whose structure could not be elucidated. The polysubstituted benzenes **1a–1h** were fully characterized by ^{1}H and ^{13}C NMR, MS, IR spectra and elemental analysis, and their structures were confirmed by single-crystal X-ray diffraction studies performed for **1a**, **1b**, **1c**, and **1h**.[9,12] As an example the structure of **1h** is shown in Fig. 1. The most unusual feature of the structure of **1a–1h** is the fact that the two aryl substituents are in *ortho* position, which has not been observed to date in any of the known cyclization reactions of malononitrile with formation of carbocyclic and heterocyclic compounds.[10–13]

To optimize the reaction conditions for the formation of the polysubstituted benzenes, the influences of base catalyst, solvent and the ratio of the components were investigated using the reaction of *p*-chlorobenzaldehyde as an example.

Ethyl α-bromoacetate can be replaced by ethyl α-chloroacetate, affording **1c** in *ca.* 47% yield. In addition to the one-pot four-component procedure described above, combinations containing plausible reaction intermediates were also tested, *viz.* (1) a mixture of previously prepared *N*-ethoxycarbonylmethylpyridinium bromide, *p*-chlorobenzaldehyde and malononitrile; (2) pyridine, ethyl α-bromoacetate and previously prepared *p*-chlorobenzylidene malononitrile; (3) *N*-ethoxycarbonylmethylpyridinium bromide and *p*-chlorobenzylidenemalononitrile. Similar results were observed in each case and nearly the same yield of **1c** was produced in these three reactions. These findings clearly show that the final polysubstituted benzene derivative **1c** results from the reactions of



Scheme 1 One-pot multi-component reaction affording polysubstituted benzene derivatives.

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Table 1 One-pot four component reactions for the synthesis of **1a–1h**

Entry	Comp	Ar	*T* (h)	Yield (%)	Mp. (°C)
1	**1a**	Ph	18	31	151–152
2	**1b**	*p*-$CH_3C_6H_4$	24	37	190–191
3	**1c**	*p*-ClC_6H_4	12	53	231–232
4	**1d**	*m*-ClC_6H_4	12	45	201–202
5	**1e**	*p*-BrC_6H_4	12	44	252–253
6	**1f**	*m*-BrC_6H_4	12	36	187–188
7	**1g**	*o*-BrC_6H_4	12	31	171–172
8	**1h**	*p*-*tert*-BuC_6H_4	12	46	184–185

N-ethoxycarbonylmethylpyridinium bromide with *p*-chlorobenzylidenemalononitrile, which are both formed *in situ*.

To explain the mechanism of this one-pot multicomponent tandem reaction, we propose a plausible reaction course, which is illustrated in Scheme 2. The first step is the formation of the two reaction intermediates already identified by the experiments described in the preceding paragraph, namely the *N*-ethoxycarbonylmethylpyridinium salt (**A**) formed from the addition of ethyl α-bromoacetate to pyridine and the arylidenemalononitrile (**B**) formed by the Knoevenagel condensation of the respective aromatic aldehyde with malononitrile. The second step is a Michael addition of a pyridinium ylide (**C**) which is formed by deprotonation of the *N*-ethoxycarbonylmethylpyridinium species (**A**) by excess pyridine to the arylidenemalononitrile (**B**) to afford a cyclopropane derivative (**D**). The third step is initiated by deprotonation and leads to the ring-opening of the activated cyclopropane (**D**) to form a 1,3-dipolar intermediate (**E**), which in turn reacts with a second equivalent of arylidenemalononitrile (**B**) with concomitant intramolecular addition of the cyano-stabilized carbanion to one of the cyano groups to give a six-membered carbon ring system (**F**). The final step is an aromatization process to form the polysubstituted benzene product **1** by elimination of one hydrogen cyanide molecule. Here the key step is that the ring-opened intermediate (**E**) undergoes a reaction formally analogous to 1,3-dipolar additions to double bonds due to inherent strain and unique electron features, which now have been utilized to synthesize valuable five- and six-membered heterocycles of potential biological relevance.[14] The unique properties of the two cyano groups in malononitrile are a crucial factor in the reaction sequence, especially in the final steps, where the cyano group acts as a strongly electron-withdrawing

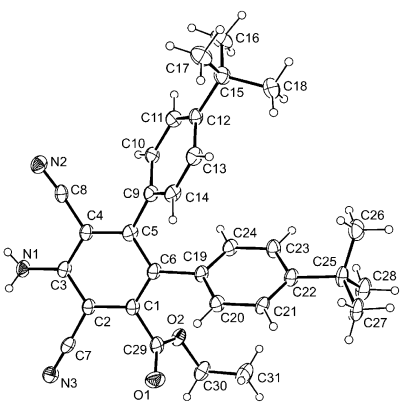
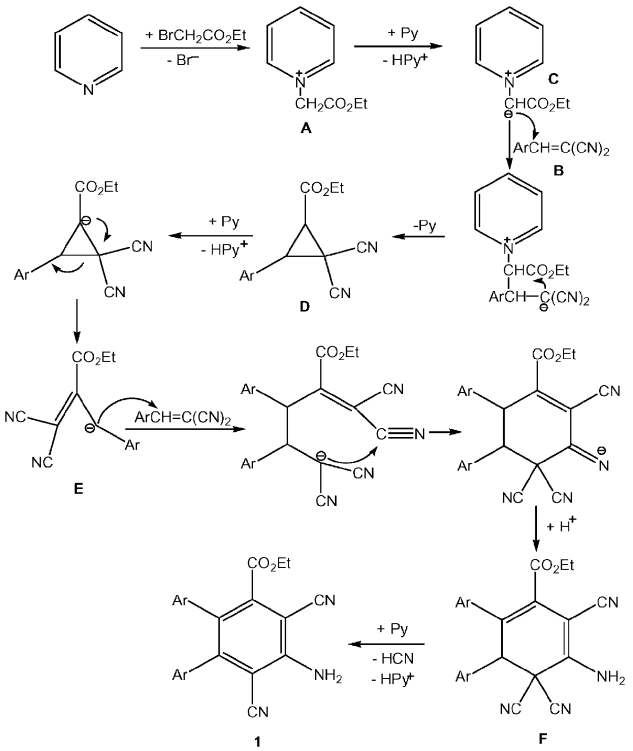


Fig. 1 Molecular structure of **1h** in the crystal.



Scheme 2 Proposed mechanism for the formation of polysubstituted benzenes **1**.

substituent, as a leaving group and as a polar triple bond for nucleophilic addition.

In order to probe the credibility of our proposed mechanistic scheme and shed more light on the formation of the polysubstituted benzenes **1**, further experiments were carried out. Firstly, when the four-component reaction was conducted at lower temperature with triethylamine as base catalyst the cyclopropane derivatives **D** (ethyl 2,2-dicyano-3-aryl cyclopropanecarboxylate) turned out to be formed in high yield. For example *p*-chlorobenzaldehyde and *o*-bromobenzaldehyde give **D1** (Ar = *p*-ClC_6H_4, 85%) and **D2** (Ar = *o*-BrC_6H_4, 75%), respectively.[15] donor–acceptor-substituted cyclopropanes of this type, which correspond to the proposed intermediate **D** in Scheme 2, were previously prepared by cyclopropanation reactions of phosphorus,[16] sulfur,[17] ammonium[18] and also pyridinium ylides.[19–20]

Secondly, when a mixture of cyclopropane derivative **D1** and *p*-chlorobenzylidenemalononitrile was heated in acetonitrile in the presence of pyridine, the expected polysubstituted benzene **1c** was obtained in 52% yield. This fact clearly shows that the ring-opening process of the cyclopropane intermediate (**D** in Scheme 2) is a key step in the multicomponent reaction. When the bulkier *p*-*tert*-butylbenzaldehyde was used in the reaction and the refluxing time was shortened to five hours, the six-membered ring system intermediate (**F**, Ar = *p*-*tert*-BuC_6H_4) could be isolated in 22% yield.[21] Quantitative conversion of this compound to **1h** proved to be possible by prolonged heating in a mixture of acetonitrile and pyridine. Fortuitously, we have been able to obtain the crystal structures of representative examples of the cyclopropane intermediate (**D**) and the six-membered ring system intermediate

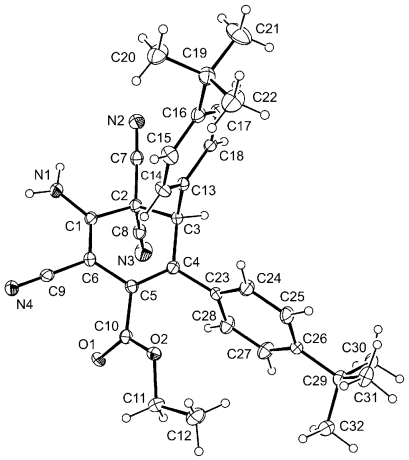


Fig. 2 Molecular structure of intermediate **F** in the crystal.

(**F**,[21] Fig. 2) as well as the final polysubstituted benzenes **1**. The mechanism proposed in Scheme 2 is strongly supported by the isolation of key intermediates, which were structurally characterized by X-ray diffraction.

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Notes and references

‡ Typical procedure: A mixture of pyridine (20.0 mmol, 1.58 g), ethyl α-bromoacetate (4.0 mmol, 0.668 g), *p*-chlorobenzaldehyde (4.0 mmol, 0.562 g) and malononitrile (4.0 mmol, 0.264 g) in acetonitrile (20 mL) was refluxed for 12 h. The solvent was removed by evaporation and the residue was titrated with ethanol (10 mL) to give the crude product, which is recrystallized in ethanol to give light yellow solid **1c** (0.458 g, 53%): Mp. 231–232 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.26 (d, J = 7.8, 2H, *p*-ClC_6H_4), 7.16 (d, J = 8.4, 2H, *p*-ClC_6H_4), 6.99 (d, J = 7.8, 2H, *p*-ClC_6H_4), 6.86 (d, J = 8.4, 2H, *p*-ClC_6H_4), 5.42 (s, 2H, NH_2), 4.13 (q, J = 7.2, 2H, CH_2), 1.05 (t, J = 7.2, 3H, CH_3) ppm. ^{13}C NMR ($CDCl_3$, 150 MHz) δ 162.8, 148.8, 147.1, 139.5, 132.4, 132.4, 129.6, 129.5, 129.2, 126.7, 125.2, 121.6, 120.3, 112.4, 111.7, 97.5, 92.9, 60.7, 11.4; IR(KBr) ν 3469, 3351, 3244, 2221, 1743, 1642, 1557, 1493, 1447, 1375, 1276, 1218, 1016, 789, 743 cm^{-1}; Anal. Calcd for $C_{23}H_{15}Cl_2N_3O_2$: C 63.32, H 3.47, N 9.63; Found: C 63.09, H 3.22, N 9.54%.

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