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An efficient one-pot synthesis of strongly fluorescent (hetero)arenes polysubstituted with amino and cyano groups

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ABSTRACT

An efficient one-pot synthesis simultaneously results in three types of densely substituted mono-, di- and tetracyclic π-systems, which can easily be isolated. Each chromophore presents a strong fluorescence emission, either in the red, green or blue part of the spectrum.

1. Introduction

The creation and stereospecific functionalization of π-systems represent an important and fundamental challenge in organic chemistry.[1] From this perspective, Burke and Schreiber recently reviewed the diversity-oriented synthesis (DOS) concept, which aims for the efficient preparation of small molecules having skeletal and stereochemical diversity and complexity of high levels.[2–4] The subject requires one to identify complexity-generating reactions that rapidly assemble different and also intricate molecular skeletons while sharing some common inherent chemical reactivity. As a case in point, Schreiber et al. used this approach for the transformation of the specific Fallis-type[3] triene substrate into a collection of products with different molecular skeletons, all based on the action of different reagents.[4] Such reagent-based transformations are referred to as differentiating processes.

Alternatively, a diversity of molecular skeletons can be accessed starting with only one set of substrate, diversity generating actions then take place in parallel processes during the reaction sequence. Furthermore, a combination of such multiple reaction steps into a sequence without isolation offers an additional advantage to achieve brevity and efficiency of the synthetic pathway. It is because of the rate at which molecular intricacy is increased, that domino/cascade reactions have received considerable attention from the synthetic organic community.[5] It is equally clear that for multisubstituted compounds, the control of both regio- and chemoselectivity also arises as a crucial factor, which even becomes more difficult in compounds containing a number of similar functional groups.

To underscore the above issues, we have been exploring a strategy for the construction of densely substituted aromatic and heteroaromatic molecules with specific domino/cascade reactions while combining several steps of bond-forming sequences into a one-pot operation. Thereby, derivatives of penta-1,4-diyn-3-one were reacted under mild conditions with malononitrile in the presence of triethylamine (Scheme 1). Remarkably, this one-pot strategy yields, at the same time, three aromatic (6+10 π-, 10 π- and 6 π-electrons), densely substituted (poly)cyclic substances based on either a novel tetracyclic skeleton (**1**) or a naphthalene (**2**) or a benzene (**3**) core. Interestingly, in **1**, the two heterocycles, pyrimidine and pyrrole, are fused to each other and then to the isoindole unit and therefore, one needs to identify the new molecular-skeleton parent as pyrrolizine.[6] We report the first representative of this new class of heteroacene, benzo[*a*]pyrimido[2,1,6-*cd*]pyrrolizine.

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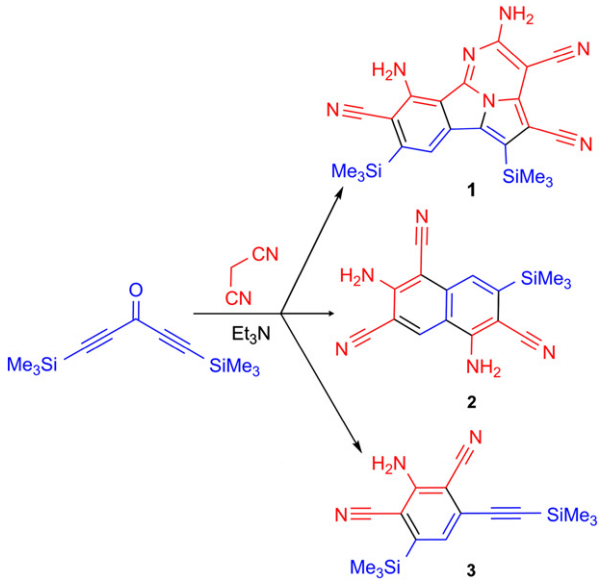
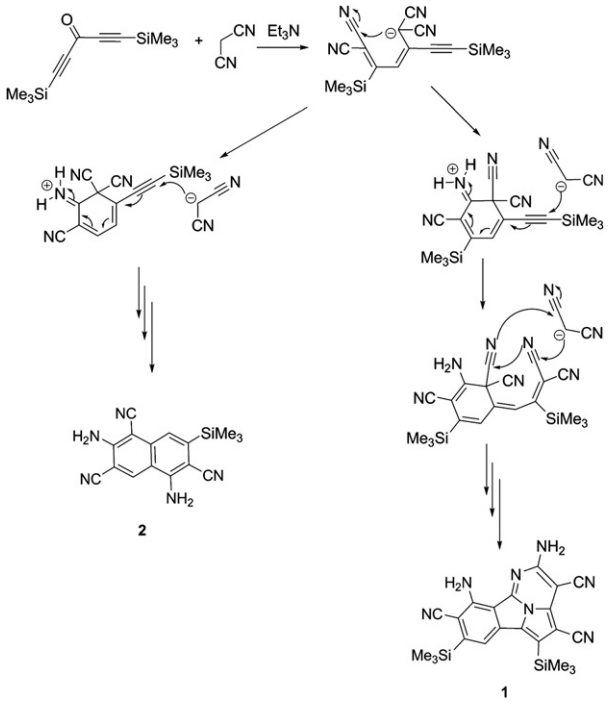


Scheme 1. The one-pot and parallel synthetic routes to chromophores **1**–**3**.



Scheme 2. Most plausible mechanisms for the formation of **1**–**2**.

2. Results and discussion

Recently, we probed the base-catalyzed reactivity of malononitrile with a series of penta-1,4-diyn-3-one derivatives and isolated a range of 2,6-dicyanoanilines (**3** and analogues).[7] Although diversifications at positions C3, C4 and C5 of the dicyanoaniline core have produced a large number of compound libraries,[8] up to now there have no examples been reported with the acetylenic functionality. In fact, an alkynyl residue is difficult to handle during multicomponent coupling methods since it opens many pathways for side reactions. Importantly, a type-**3** compound offers a useful functionality for Sonogashira coupling reactions and conjugate additions. First attempts along this line resulted in a novel π-conjugated anion, (*E*)-3-(3-amino-2,4-dicyanophenyl)-1,1-dicyanoprop-2-en-1-ide.[9] It was on this basis that we have undertaken a detailed investigation on the reaction of 1,5-bis(trimethylsilyl)penta-1,4-diyn-3-one with malononitrile in the presence of Et_3N as catalyst. It turned out that three different compounds (**1**–**3**) form via a one-pot reaction. Notably, compound **2** reveals a dense substitution pattern where electronic donor (NH_2) and acceptor (C≡N) groups are mixed, a result, which could hardly be achieved otherwise, e.g., through substitution reactions on a naphthalene core.[10] The same clearly holds for **1** as well.

As we discussed in our previous paper,[7] the formation of **3** starts either with a Knoevenagel condensation of a penta-1,4-diyn-3-one with malononitrile and/or with its conjugate addition followed by a conjugate addition with a second equivalent of malononitrile leading to the tautomeric intermediates. A further conjugate addition of malononitrile and consecutive Thorpe–Ziegler cyclizations together with an elimination of 1,1,1-tricyanomethyl affords **3**. However and most importantly, one acetylenic group stays intact during the reaction process for **3**. Now, it is reasonable that the acetylenic group from the tautomeric intermediates can alternatively undergo a further cycloaddition with malononitrile to afford **2**, while a participation of the carbonitrile in *ortho*-position to the acetylenic substituent leads to the formation of **1** (Scheme 2). Their yields can be individually optimized between 15% and 70% depending on the reaction conditions. Increasing the molar ratio of malononitrile and 1,5-bis(trimethylsilyl)penta-1,4-diyn-3-one from 4:1 to 10:1 has no substantial effect on the outcome of the reaction. A comparison of heating and microwave irradiation indicates that the latter in toluene apparently shortens the reaction time, but gives comparable yields (Table 1). However, the microwave irradiation in CH_2Cl_2 improved the yield of **1** substantially. It is worth mentioning that the reaction of malononitrile with a ketone in the presence of Al_2O_3 or β-alanine as catalyst only afforded the corresponding dicyanodiethynylethene.[11] Obviously, Et_3N plays a key role in the formation of **1**–**3**.

Crystallizations of products **1**–**3** from $CH_2Cl_2/CHCl_3$, CH_3OH and CH_2Cl_2, respectively, gave crystals in the form of different solvates suitable for X-ray analysis. Both compounds **1** and **3** crystallize in the triclinic crystal system, space group *P*-1, and **2** in the monoclinic crystal system, space group $P2_1/c$ (Fig. 1). The structural data of **3** have recently been reported.[7] In accordance with their aromaticity, all molecules have planar geometries; largest deviations from the least-squares planes [all atoms excluding the $Si(Me)_3$] are 0.055(5) Å for atom N3 for **1**, and 0.047(2) Å for atom C1 for **2**. The bond lengths of the skeleton of **2** agree well with the reported data for naphthalene.[12] The tetracyclic core of **1** may structurally best be compared with the indolizino[3,4,5-*ab*]isoindole skeleton.[13] In an analogous manner, one can divide the skeleton of **1** into two aromatic fragments, a benzene and a pyrrolopyrimidine, and this is reflected by the connecting bond distances, C4–C5 and C11–C12, which accordingly are relatively long: 1.439 Å and 1.477 Å.

The UV–vis spectra of the chromophores **1**–**3** recorded in CH_2Cl_2 show strong absorption bands in the UV, but also strikingly intense absorption bands in the visible region, lying in the yellow, blue and near-UV, respectively (Fig. 2). Upon photoexcitation, compounds **1**–**3** show strong red, green and blue fluorescence with quantum yields of 72%, 52% and 25%, respectively. These high quantum yields compare well with those of the above-mentioned isoindole

Table 1
A comparison of heating and microwave irradiation applied for the reaction[a]

	1	2	3
Microwave (120 °C, 10 min)	13.2 mg (6%)	22.1 mg (14%)	87.0 mg (56%)
Heat (120 °C, 2 h)	14.2 mg (7%)	23.8 mg (16%)	104.3 mg (67%)

[a] 1,5-Bis(trimethylsilyl)pent-1,4-diyn-3-one/malononitrile/triethylamine=0.5 mmol/2.0 mmol/0.5 mmol in 3 ml toluene.

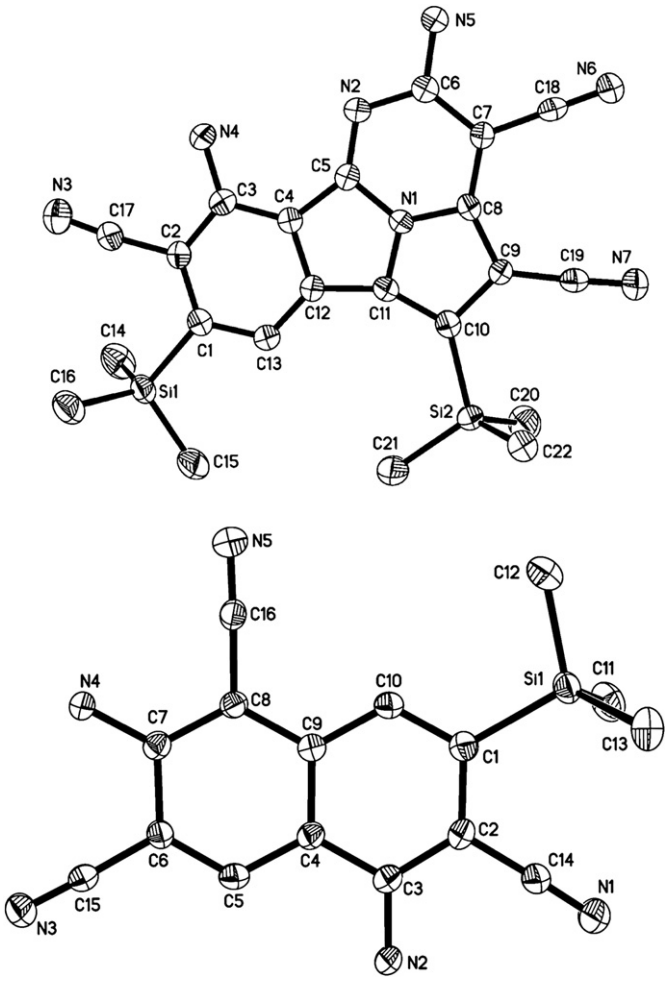


Figure 1. X-ray crystal structures of **1** (top) and **2** (bottom) (ORTEP, thermal ellipsoids set at the 50% probability level). Hydrogen atoms and solvents are omitted for clarity.

derivatives.[13] The emission maxima lie at 17,300 cm^{-1} (578 nm), 20,500 cm^{-1} (488 nm) and 24,700 cm^{-1} (405 nm). The fluorescence excitation spectra, measured at 630, 550 and 430 nm emission wavelengths, agree well with the corresponding absorption profiles. The blue shifts in both the absorption and emission bands on going from **1** to **3** are not unexpected on the basis of the decreased size of the π-conjugated frameworks.

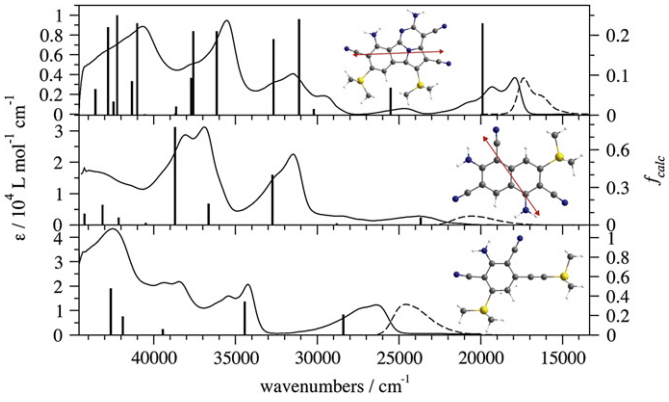


Figure 2. Electronic absorption (solid line) and fluorescence emission (dashed line) spectra of **1**–**3** in deaerated dichloromethane solution at room temperature, together with the calculated oscillator strengths. The arrows indicate the $S_0 \rightarrow S_1$ transition dipole moment orientations.

To understand the ground and excited state electronic properties of chromophores **1**–**3**, density functional theory (DFT) as well as time-dependent DFT (TD-DFT) calculations was performed with the B3LYP functional and the TZVP basis set with TURBOMOLE V5.9.[14] In each case, the minimum-energy geometry is calculated to have C_s symmetry. The central aromatic framework is planar in both S_0 ground and S_1 excited states. The former is in line with the corresponding crystal structures.

For **1**, the vertical TD-DFT calculations predict the electronic $S_0 \rightarrow S_1$ excitation to be an intense ππ* transition at 19,900 cm^{-1} (503 nm) with an oscillator strength f_{calcd}=0.23, as shown with the stick spectrum in Figure 2. Both the transition energy and intensity are in fair but still acceptable agreement with the longest-wavelength absorption, for which the 16,530–19,230 cm^{-1} energy-integrated absorption yields an oscillator strength f_{exp}=0.04. According to the TD-DFT calculation, the $S_0 \rightarrow S_1$ electronic excitation is dominated by the HOMO→LUMO contribution (95%), which corresponds to redistribution of π-electron density over the main part of the molecular skeleton (Fig. 3).

For **2**, the vertical TD-DFT calculations predict the electronic $S_0 \rightarrow S_1$ excitation to be a ππ* transition at 23,700 cm^{-1} (422 nm) with f_{calcd}=0.06. Both the transition energy and intensity are in very good agreement with the longest-wavelength absorption, for which the 20,000–26,700 cm^{-1} energy-integrated absorption yields an oscillator strength f_{exp}=0.04. The $S_0 \rightarrow S_1$ excitation is dominated (97%) by the HOMO→LUMO contribution. As Figure 4 shows, the π-electron charge transfer occurs mainly from the two amino groups towards the naphthalene core and the cyano group C15–N3 (Fig. 1). This transition is qualitatively similar to that of the $S_0 \rightarrow S_1$ excitation recently reported for **3**.[7] There, the intense (f_{exp}=0.16, f_{calcd}=0.21) ππ* excitation, calculated at 28,400 cm^{-1} (352 nm), also has strong intramolecular π charge transfer character from the amino group to the proximal cyano groups.

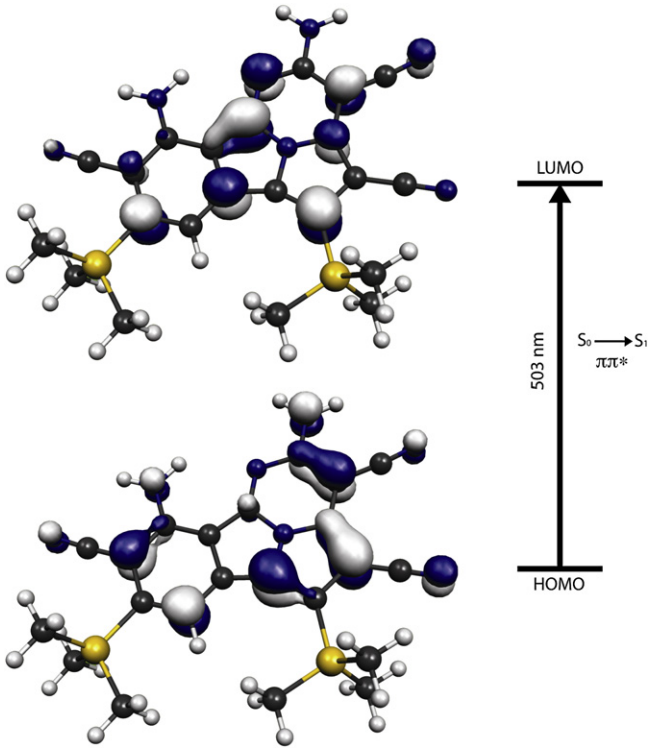


Figure 3. The HOMO and LUMO of **1** that are involved in the lowest-energy ππ* transition.

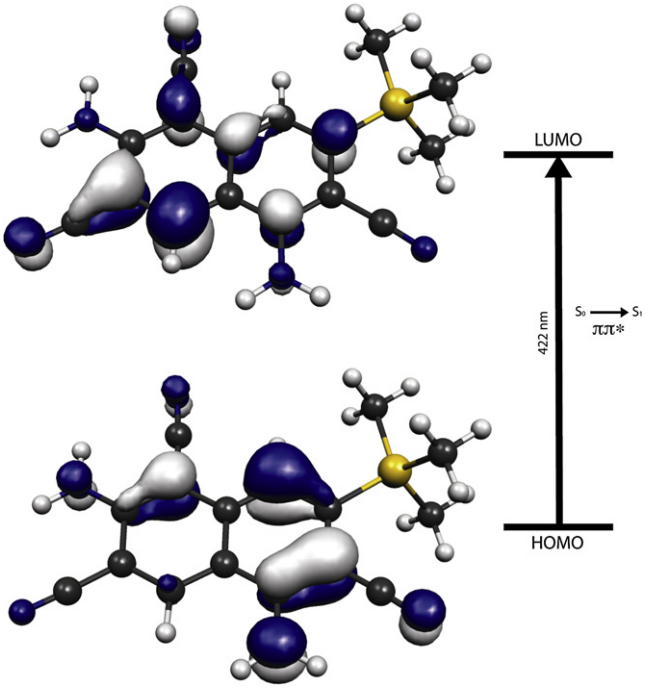


Figure 4. The HOMO and LUMO of **2** that are involved in the lowest-energy ππ* transition.

3. Conclusion

In summary, we have shown the base-catalyzed reactivity of malononitrile with 1,5-bis(trimethylsilyl)penta-1,4-diyn-3-one, leading to the formation of three densely substituted fluorescent (hetero)arenes via a one-pot reaction. This novel sequence of cycloadditions offers a new route to functionalized (hetero)arenes that would be difficult to produce conventionally, especially that corresponding to the tetracyclic core of **1**. Further studies on the generality and application of this type of reaction to produce polycyclic substances with different functional groups are in progress.

4. Experimental

4.1. Equipment

^{1}H and ^{13}C NMR spectra were obtained on a Bruker AC 300 spectrometer operating at 300.18 and 75.5 MHz, respectively: chemical shifts are reported in parts per million relative to TMS. The following abbreviations were used: s (singlet), d (doublet), t (triplet) and m (multiplet). Melting points were determined using a Büchi 510 instrument and are uncorrected. ESI-MS was carried out with an FTMS 4.7 TBioAPEX II TOF apparatus. Photophysical measurements were performed on solutions of **1**–**3** in CH_2Cl_2 at room temperature. UV–vis absorption and emission spectra were recorded on a Perkin–Elmer Lambda 900 spectrometer and a Perkin–Elmer Luminescence spectrometer LS 50B.

4.2. Crystallography

A red plate-like crystal of **1** and an orange rod-like crystal of compound **2** were mounted on a Stoe Mark II-Imaging Plate Diffractometer System[15] equipped with a graphite monochromator. In each case, data collection was performed at −100 °C using Mo Kα radiation (λ=0.71073 Å). Two hundred and forty exposures (3 min per exposure) were obtained at an image plate distance of 135 mm, 180 frames with φ=0° and 0°<ω<180° and 80 frames with φ=90° and 0<ω<80°, with the crystal oscillating through 1° in ω. The resolution was D_{min}−D_{max} 0.72–17.78 Å. The structures were solved by direct methods using the program SHELXS-97[16] and refined by full matrix least squares on F^2 with SHELXL-97.[17] The hydrogen atoms were included in calculated positions and treated as riding atoms using SHELXL-97 default parameters, except for the OH hydrogen atoms in **2**, which were found and refined. All non-hydrogen atoms were refined anisotropically. No absorption correction was applied. Crystal data have been deposited at the Cambridge Crystallographic Data Centre, CCDC-679352 (**1**), CCDC-679353 (**2**) and CCDC-656928 (**3**). Copy of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

4.3. Materials

All reagents were purchased from commercial sources and used without additional purification. 1,5-Bis(trimethylsilyl)penta-1,4-diyn-3-one was prepared according to literature procedure.[18]

4.3.1. *A conventional heating procedure*

A mixture of 1,5-bis(trimethylsilyl)penta-1,4-diyn-3-one (110 mg, 0.5 mmol), malononitrile (100 mg, 1.5 mmol) and triethylamine (50 mg, 0.5 mmol) in toluene (2.0 ml) was refluxed with stirring at 120 °C for 2 h. The solvent was removed under reduced pressure. Purification of the brownish oily residue by column chromatography on silica gel, eluting subsequently with CH_2Cl_2, CH_2Cl_2/diethyl ether (100:1 and then 100:2), gave compounds **1**–**3**, respectively.

*2,9-Diamino-5,7-bis(trimethylsilyl)benzo[a]pyrimido[2,1,6-cd]-pyrrolizine-3,4,8-tricarbonitrile (**1**).* As a red solid. Yield 13 mg (6%). 286 °C (dec). ^{1}H NMR (CD_2Cl_2) δ: 7.53 (s, 1H), 6.04 (s, 2H), 5.86 (s, 2H), 0.60 (s, 9H), 0.48 (s, 9H). Selected IR data (KBr, cm^{-1}): 3436, 2924, 2854, 2203, 1632, 1460, 1242, 844. MS (ESI-TOF): $[M]^+$ calcd 411.1553; found 411.1561.

*2,5-Diamino-7-(trimethylsilyl)naphthalene-1,3,6-tricarbonitrile (**2**).* As a pale yellow solid. Yield 20 mg (13%). 212 °C (dec). ^{1}H NMR (CD_3OD) δ: 8.69 (s, 1H), 7.22 (s, 1H), 0.43 (s, 9H). ^{13}C NMR (CD_3OD) δ: 153.00, 152.35, 147.87, 139.16, 136.49, 119.91, 118.27, 116.48, 116.21, 114.54, 99.52, 91.18, 89.53, −1.65. Selected IR data (KBr, cm^{-1}): 3435, 2923, 2852, 2206, 1631, 1453, 1121, 844. MS (ESI-TOF): $[M+H]^+$ calcd 306.1175; found 306.1186.

*2-Amino-4-(trimethylsilylethynyl)-6-(trimethylsilyl)benzene-1,3-dicarbonitrile (**3**).*[7] As a white solid. Yield 110.5 mg (70%). Mp 122–124 °C. ^{1}H NMR ($CDCl_3$) δ: 6.97 (s, 1H), 5.15 (s, 2H), 0.41 (s, 9H), 0.30 (s, 9H). ^{13}C NMR ($CDCl_3$) δ: 152.93, 152.90, 131.81, 128.13, 118.34, 116.43, 107.34, 102.31, 102.20, 102.08, 1.22, 0.002. Selected IR data (KBr, cm^{-1}): 3479, 3362, 2959, 2924, 2218, 2160, 1735, 1637, 1538, 1403, 1253, 1062, 946, 845, 759, 671. MS (ESI-TOF): $[M+Na]^+$ calcd 334.1172; found 334.1171.

4.3.2. *A microwave assisted synthesis*

In the presence of triethylamine (50 mg, 0.5 mmol), a mixture of 1,5-bis(trimethylsilyl)pent-1,4-diyn-3-one (110 mg, 0.5 mmol) and malononitrile (120 mg, 1.8 mmol) in 2 ml of CH_2Cl_2 was treated under microwave irradiation (110 °C, 10 min). Following the same work-up procedure as stated above, pure compounds **1**–**3** were obtained in yields of 15% (30 mg), 10% (16 mg) and 52% (82 mg), respectively.

Acknowledgements

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