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Solid-phase combinatorial syntheses of mesomorphic 4-alkoxyphenyl 4-alkoxybenzoylaminobenzoates

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Eighteen two-ring and 100 three-ring benzenoid amides were synthesised using a solid-phase combinatorial method involving acylation or benzoylation and palladium(0)-catalysed carbonylation of a secondary amine, obtained by the reductive amination of 4-iodoaniline and a backbone amide linker. The purity of the products obtained was high enough for investigation of their thermal properties. All the three-ring derivatives were shown to be mesomorphic, but the two-ring derivatives were not. The mesomorphic behaviour and the transition temperatures of the three-ring derivatives were virtually identical to those of samples obtained by liquid-phase synthesis and purified by column chromatography and recrystallisation.

Keywords: solid-phase combinatorial synthesis; three-ring benzenoid amides; reductive amination; palladium(0)-catalysed carbonylation

1. Introduction

Combinatorial chemistry is a very valuable tool for the synthesis of libraries of new compounds. It has been utilised in a number of research fields, including the synthesis of drugs, bioactive molecules, catalysts and other functionalised molecules [1, 2]. By employing combinatorial chemistry in solution, a library of liquid crystals based on fluorinated *p*-quaterphenyls has been generated [3]. The use of solid-phase combinatorial synthesis in liquid crystals research has, however, been limited. The present authors have previously investigated solid-phase combinatorial synthesis to form libraries of liquid crystals containing a seven-membered core [4], conventional rod-like structures based on azomethine [5, 6] or isoxazole [7], as well as banana-shaped molecules [8, 9].

In general, liquid crystals comprise a rigid core and one or two flexible side-chains [10]. It is well known that both mesomorphic properties and thermal behaviour may be modified merely by changing the length of the side-chain. After the rigid core structure has been fixed, it is common practice to adjust the length of the side-chain until the required mesomorphic properties have been obtained. In practical terms, we have often had to discard synthetic molecular design, since this approach often takes too much time and effort for the construction of a library of liquid crystals.

We have recently reported the solid-phase synthesis of a library of seven-membered troponoid liquid crystals, using an amide group derived from one of the trivalent arms of a nitrogen atom, connected to a solid support [4]. The amide chromophore is regenerated in troponoid amides by cleavage from the solid support at the final stage.

One of the most important features of solid-phase combinatorial synthesis is the selection of the linker used to load molecules on to the solid support. The linker should retain molecules safely on the solid support during reactions. After the reactions are completed, the product must be quickly and efficiently removable from the solid support without damage to the products, by the use of a readily removable cleavage reagent such as trifluoroacetic acid (TFA). Ideally, traceless linkers should be used which do not remain in the loading site of the product. The selection of an appropriate linker system is therefore essential for successful synthesis, not only for producing a library of liquid crystals but also for other synthetic targets. In addition, reaction on a solid support has the advantage of simplifying purification of the product, since excess reactant can be readily removed by filtration. Finally, products on the solid support can be purified by washing with a suitable solvent.

In the present paper we describe the creation at high purity of a new library of liquid crystals with a benzenoid–amide structure, using solid-phase combinatorial synthesis and conversion without further purification [11]. The reason for selecting two types of two-ring benzenoid amides, **1** and **2,** and a three-ring benzenoid amide, **3,** was that the nitrogen atom

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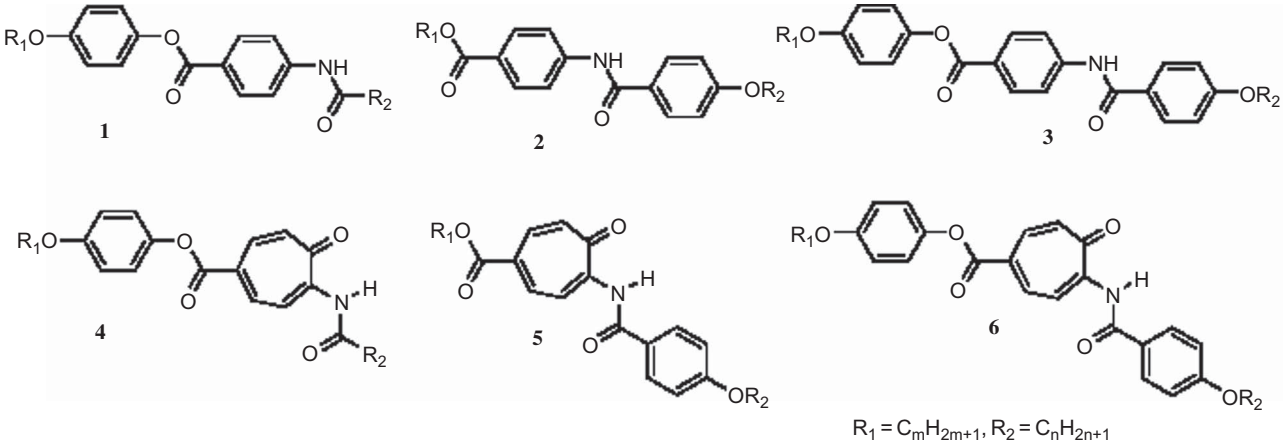
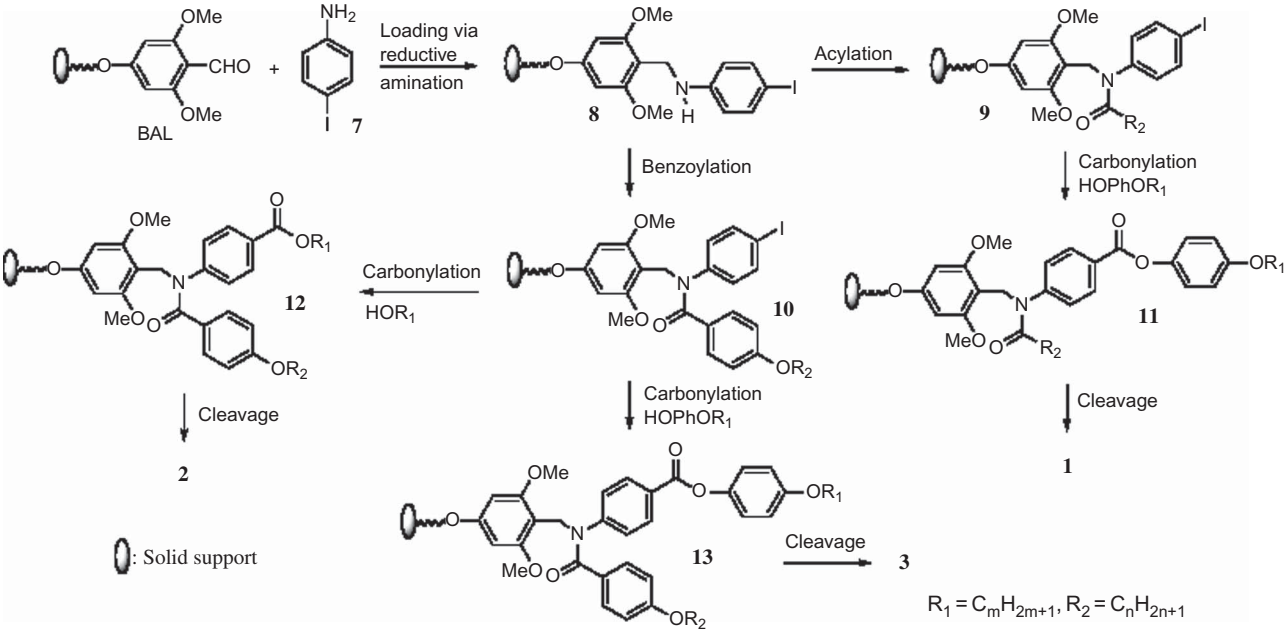


Scheme 1. Compounds under investigation.



Scheme 2. Synthetic strategy for two- and three-ring benzenoids.

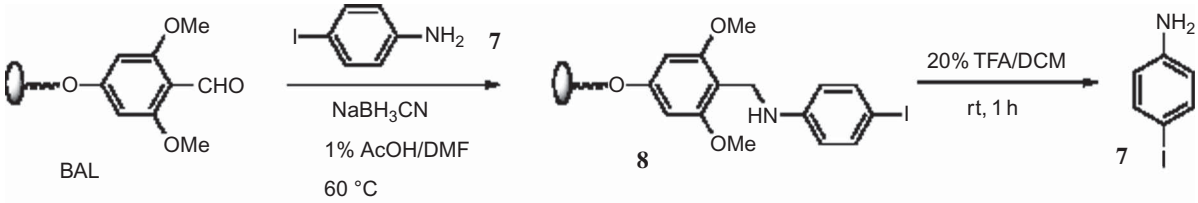
could be used as the connection point for the solid support, but would not remain as the connecting site in the final product. Finally, it would be possible to compare the thermal behaviour of the benzenoid amides, **1**, **2**, and **3**, with that of the troponoid amides (**4**, **5** and **6**) which had been previously obtained by solid-phase combinatorial synthesis [4] (Scheme 1).

Scheme 2 shows the synthetic plan for **1**, **2**, and **3** using solid-phase synthesis. 4-Iodoaniline (**7**) was loaded on to a backbone amide linker (BAL) to form a secondary amine, **8,** in the presence of sodium cyanoborohydride ($NaBH_3CN$) by reductive amination [12]. Reaction of **8** with acyl or 4-alkoxybenzoyl chlorides gave acylated products, **9,** and benzoates, **10**, respectively. The acylated products, **9,** were converted to **11** by carbonylation with 4-alkoxyphenols under an atmosphere of carbon monoxide in the presence of a palladium(0) catalyst [13]. Similarly, carbonylation of benzoates **10** with alcohols and 4-alkoxyphenols yielded **12** and **13**, respectively. Finally, cleavage of the carbonylated products **11**–**13** with TFA gave the two types of two-ring amides, **1** and **2,** and the three-ring amide, **3**, respectively.

2. Results and discussion

2.1 Synthesis

Scheme 3 shows the result of loading **7** on to BAL (D-series lantern) by reductive amination. The

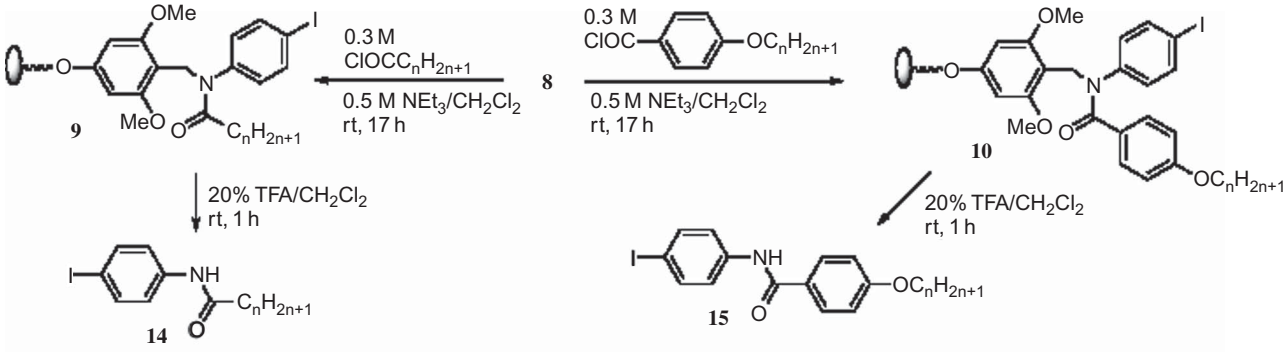


Reaction conditions and conversion to **8**

Entry	$NaBH_3CN$ (M)	Time (h)	Conversion (%)
1	0.05	17	38
2	0.05	34	41
3	0.1	17	35

Note: Purity is >99%.

Scheme 3. Loading of 4-iodoaniline, **7**, on BAL.



Purity of **14**

n	Purity (%)	MS (m/z)[a]
5	99	318.0
9	95	374.0
13	93	430.0

Note: Conversion is >99%. [a][M+H]$^+$.

Purity of **15**

n	Purity (%)	MS (m/z)[a]	*n*	Purity (%)	MS (m/z)[a]
1	98	354.0	6	99	424.1
2	99	368.0	7	99	438.1
3	98	382.0	8	98	452.1
4	99	396.1	9	95	466.1
5	89	410.1	10	99	480.1

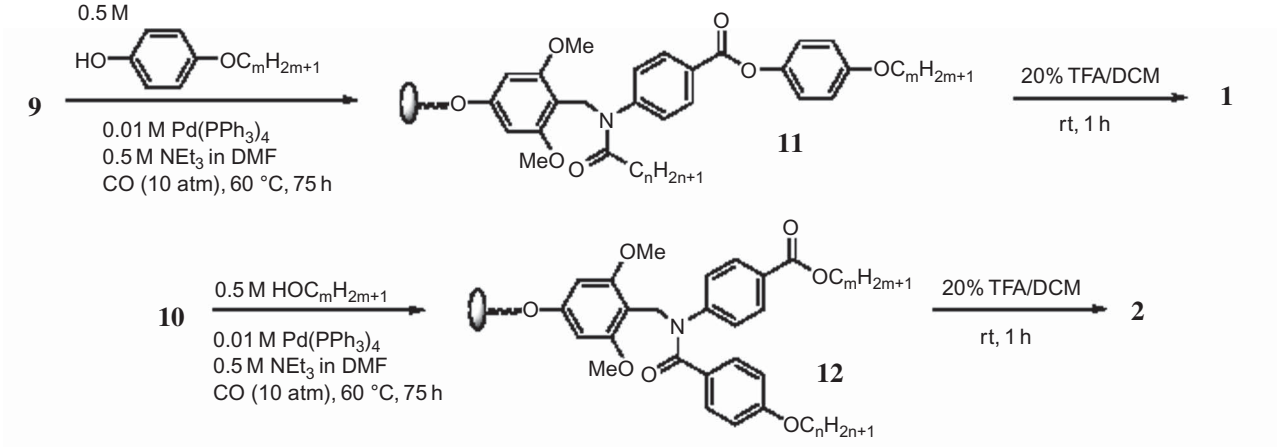
Note: Conversion is >99%. [a][M+H]$^+$.

Scheme 4. Acylation and bezoylation on a solid support.

reaction conditions of Entry 2 were best. The conversion and purity of **8** were determined by high-performance liquid chromatography (HPLC) and estimating the amount of **7** recovered after cleavage of **8** with 20% TFA in dichloromethane. Although compounds **7** obtained by solid-phase synthesis were not purified, their purity was adequate for the subsequent reactions.

Amine **8** was reacted with acyl chlorides and 4-alkoxybenzoyl chlorides in the presence of triethylamine to give lanterns **9** and **10**, respectively. The conversion and purity of the resulting acylated and benzoylated compounds are shown in Scheme 4. The conversion was assessed from the amount of 4-iodo-1-alkanoylaniline (**14**) and 4-iodo-1-(4-alkoxybenzoyl)aniline (**15**) obtained after cleavage of lanterns **9** and **10**. The conversion and purity of the acylated and benzoated products were sufficient for the subsequent reactions.

Carbonylation of lantern **9** with 4-alkoxyphenols in the presence of tetrakis(triphenylphosphine)palladium(0) and triethylamine under an atmosphere of carbon monoxide gave the corresponding lantern, **11**, whereas carbonylation of **10** with alcohols gave **12**. The conversion and purity of **1** and **2** were determined after cleavage of **11** and **12**, as illustrated in Scheme 5.



	m	*n*	Purity (%)	MS (m/z)[a]	mp (°C)
1	4	2	95	342.2	137
		5	97	384.2	154
		8	96	426.3	136
	8	2	92	398.2	149
		5	97	440.3	132
		8	89	482.3	124
	12	2	90	454.3	121
		5	89	496.3	128
		8	87	538.4	124

Note: [a][M+H]$^+$. Conversion is >99%.

	m	*n*	Purity (%)	MS (m/z)[a]	mp (°C)
2	5	2	96	356.2	147
		5	94	398.2	164
		8	93	440.3	148
	9	2	95	412.2	149
		5	95	454.2	168
		8	93	496.3	150
	13	2	95	469.3	146
		5	98	510.4	164
		8	92	552.4	148

Note: [a][M+H]$^+$. Conversion is >99%.

Scheme 5. Carbonylation of compounds **8** and **10**, and purity and melting points of **1** and **2**.

Scheme 6 shows the purity of the three-ring benzenoids, **3**, obtained by carbonylation of **10** with 4-alkoxyphenols via cleavage of lantern **13**. Although compounds **3** were not purified by chromatography or recrystallisation, their average purity was as high as 95%.

2.2 Mesomorphic properties

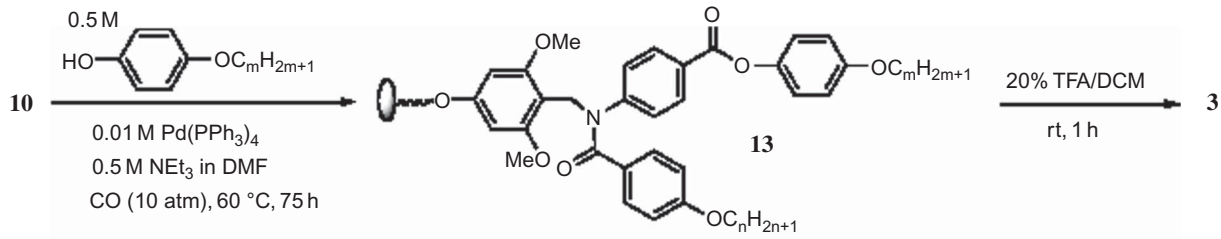
Thermal behaviour and microscopic textures were assessed using a polarising microscope equipped with hot-stage. Mesomorphic properties were not observed in the two-ring benzenoids, **1** and **2,** as shown in the tables below Scheme 5. The transition temperatures of the three-ring benzenoid amides, **3,** are summarised in Table 1, and all the derivatives were shown to be mesomorphic.

Typical textures are shown in Figures 1–3, together with those of the compounds obtained by conventional liquid-phase synthesis and purified by column chromatography and recrystallisation. Compound **3** ($m = n = 2$) showed schlieren textures with two and four brushes, which indicated nematic (N) phases, as shown in Figure 1.

Compound **3** ($m = 8$, $n = 5$), shown in Figure 2, showed homeotropic and focal–conic fan textures, indicating smectic A (SmA) phases. Compound **3** ($m = n = 8$) had two types of mesophase, as shown in Figure 3. At the higher temperature, SmA phases with homeotropic and focal–conic fan textures appeared. At the lower temperature, the homeotropic and focal–conic fan textures became schlieren and broken fan textures, respectively; these observations support the presence of smectic C (SmC) phases.

The side-chain length in **3** affected the appearance of the mesophases. The length (m) of the ester side enhanced the appearance of the SmC phase, whereas the length (n) of the amide side promoted the SmA phase.

Table 2 provides a comparison of the transition temperatures of compounds **3** obtained by solid-phase synthesis, without purification by chromatography or by recrystallisation, and those resulting from liquid-phase synthesis. In general, the purity of compounds



m \ n	1	2	3	4	5	6	7	8	9	10
1	73	99	98	96	97	89	89	92	93	88
2	98	95	99	97	98	98	86	89	92	87
3	99	99	97	98	98	98	96	97	96	89
4	91	98	96	98	97	96	93	95	93	86
5	97	98	97	97	97	89	94	99	93	87
6	99	98	98	97	97	89	93	96	95	90
7	96	99	99	97	99	91	95	97	94	90
8	88	99	99	99	99	82	97	97	97	92
9	96	99	99	99	99	88	97	98	94	86
10	94	98	99	98	98	85	99	98	97	89

Note: Conversion is >99%.

Scheme 6. Carbonylation of compound **10**, and purity (%) of **3**.

in liquid crystal libraries is required to be above 99%, which is higher than that (70–80%) for libraries of drugs [14]. Although the average purity of **3** was only 95%, the transition temperatures determined by solid-phase and liquid-phase synthesis were almost identical, with the result that the purity of **3** was seen to be sufficient to allow a survey of mesomorphic compounds. It also confirmed that solid-phase synthesis allowed a saving in time and effort.

2.3 X-ray diffraction study

An X-ray diffraction (XRD) study of compound **3** ($m = n = 8$), which exhibited SmA and SmC phases, was carried out and showed the layer spacing of the SmA phase to be 35.7 Å at 220°C, and that of the SmC phase to be 31.2 Å at 180°C. Since the molecular length was calculated to be 37.6 Å by the MM2 method, the SmA phase had a monolayer packing model, and the tilt angle of the SmC phase was calculated to be about 34° when a monolayer packing model was considered. Intermolecular hydrogen bonding is assumed to be involved in both models.

2.4 Comparison of the thermal behaviour of benzenoids and troponoids

As shown in Scheme 5, none of the two-ring benzenoids, **1** and **2,** was mesomorphic. Table 3 summarises the transition temperatures of the corresponding two-ring troponoids, **4** and **5** [4], which showed SmC phases. The melting points of benzenoids**, 1** and **2**, were higher than those of the troponoids. This is the result of intermolecular hydrogen bonding of the amide groups. Although troponoids, **4** and **5,** also contain an amide group, in this case the amide group exhibits intramolecular hydrogen bonding with the neighbouring tropone carbonyl, and this disturbs the intermolecular hydrogen bonding. These structural characteristics of the troponoids decrease the melting point and give rise to mesomorphic properties.

The transition temperatures of selected three-ring benzenoids, **3,** and troponoids, **6,** [4] are shown in Table 4. The thermal stability of the mesophases of **3**

Table 1. Transition temperatures (°C) of **3** obtained by solid-phase synthesis.[a]

m/*n*	1	2	3	4	5	6	7	8	9	10
1	K229N316I	K238N293I	K220N276I	K214N238I	K194A216N255I	K194A216N255I	K204A228N244I	K200A232N244I	K199A235N240I	K198A235N236I
2	K227N286I	K242N295I	K220N264I	K212A216N262I	K208A228N255I	K202A238N258I	K205A241N25II	K204A244N248I	K202A245I	K199A245I
3	K218N270I	K228N27II	K213A215N256I	K207A234N253I	K205A236N246I	K199A236N243I	K199A239I	K206A256I	K194A240I	K189C191A240I
4	K206N264I	K220N276I	K203A225N256I	K200A237N250I	K201A237N243I	K198A24II	K192A241I	K189A246I	K189C202A240I	K183C201A240I
5	K196N257I	K211A224N260I	K196A224N242I	K196A236N256I	K197A243N244I	K192A243I	K192A242I	K189C202A241I	K189C212A239I	K184C218A239I
6	K190N249I	K206A236N259I	K191A235N245I	K185A240N244I	K188A236I	K188A242I	K190A2371	K182C198A240I	K182C206A237I	K181C220A237I
7	K190A222N248I	K201A238N252I	K188A236N242I	K182A243I	K186A240I	K185A239I	K187A240I	K183C198A236I	K183C216A237I	K176C219A234I
8	K188A239N247I	K195A248N252I	K188A242I	K176A244I	K182A242I	K181A240I	K180A2371	K179C188A234I	K180C214A233I	K179C218A233I
9	K186A244N245I	K196A256I	K186A244I	K178A244I	K178A240I	K178A240I	K180A236I	K180C192A237I	K175C204A229I	K175C214A232I
10	K181A247I	K192A248I	K183A242I	K176A240I	K178A242I	K178A238I	K177A238I	K177C191A236I	K176C207A232I	K175C216A231I

Note: [a]K: crystals, N: nematic phase, A: smectic A phase, C: smectic C phase, I: isotropic liquid.

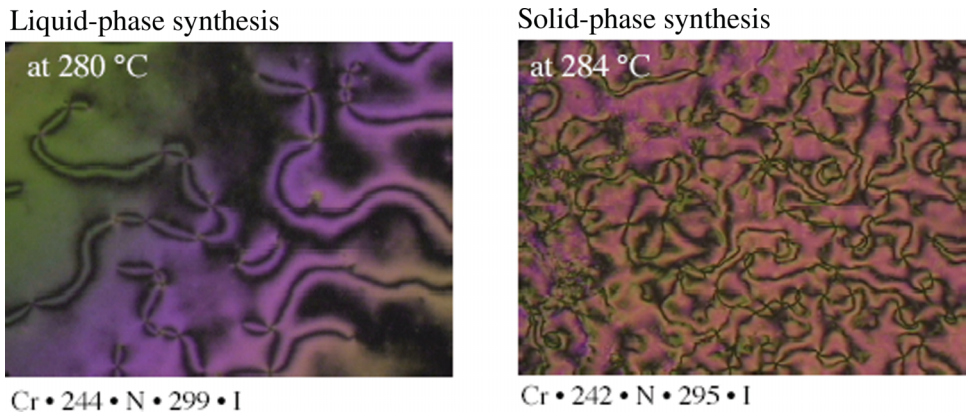


Figure 1. Texture of compound **3** ($m = n = 2$).

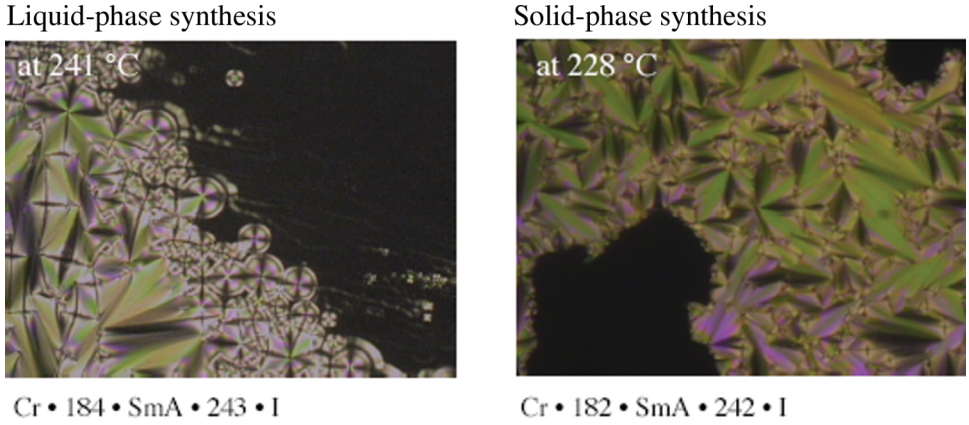


Figure 2. Texture of compound **3** ($m = 8$, $n = 5$).

was higher than that of **6**. Previously it was observed that benzenoids favoured the formation of N phases, whereas troponoids formed Sm phases [15–17]. This is explained by the fact that troponoid core structures are more polar than benzenoid cores, contributing to the formation of layer structures, not only by aligning head-to-tail structures to cancel the dipole–dipole repulsion of the troponoid cores, but also by inducing more significant microphase separation than the less polar benzenoid cores. In the case of troponoid **6**, however, there is an electron-withdrawing group at the C–5 position of the tropone structure, which reduces the polarity of its core structure, with less alignment into head-to-tail structures and less significant microphase separation. The thermal stability of the mesophases is correspondingly lower than in **3**.

2.5 Effect of the connecting group

Table 5 summarises the transition temperatures of compounds **3** and **16** [18, 19], in which the direction of the ester connecting group was different. It is seen that the thermal stability of **3** was higher than that of **16**. This is due to a difference in the acidity of the amide hydrogen. The electron-withdrawing character of the ester carbonyl group in **3** increased the acidity of the amide hydrogen atom, which in turn enhanced the strength of intermolecular hydrogen bonding, giving a higher transition temperature.

3. Conclusions

Two- and three-ring benzenoid amides (**1**–**3**) were produced by solid-phase synthesis in order to investigate their thermal behaviour. The thermal stability of **3** was higher than that of the corresponding troponoids, **6**. The troponoid core structure has an electron-withdrawing group in the C–5 position and the mesophases had lower thermal stability than the mesophases of the troponoids with an electron-donating alkoxy group at the C–5 position.

The solid-phase synthesis successfully generated a library of liquid crystals with high purity and conversion. The mesophases of **3** obtained by solid-phase synthesis exhibited the same phase transition, with

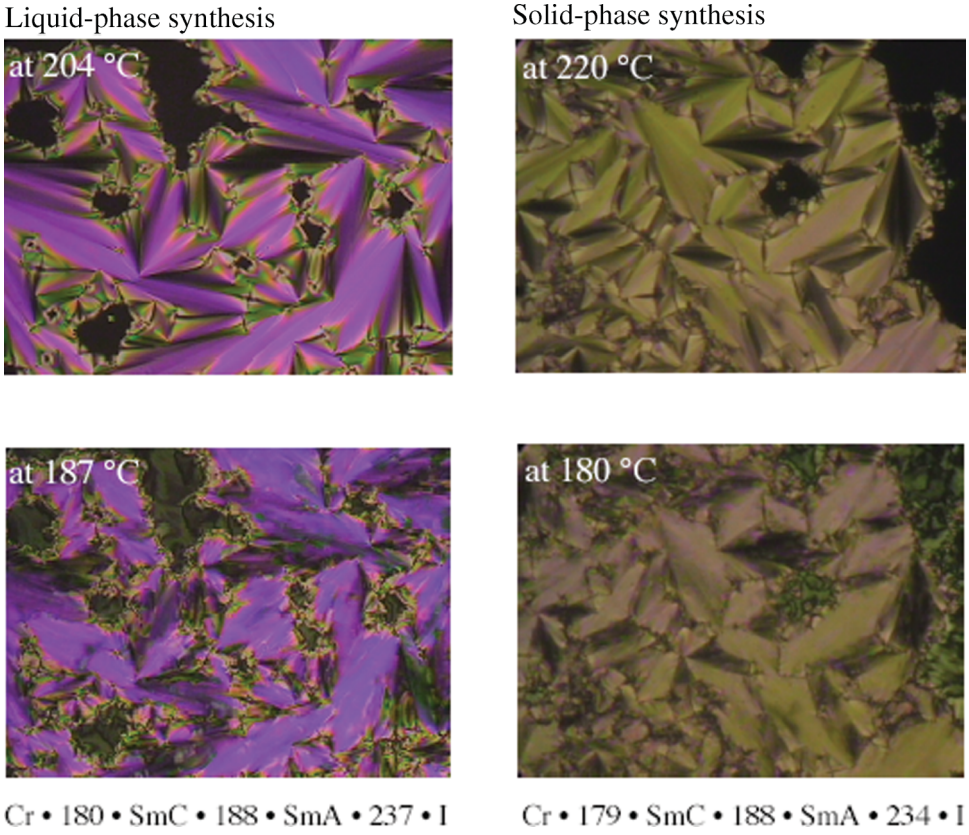


Figure 3. Texture of compound **3** ($m = n = 8$) (colour version online).

Table 2. Comparison of transition temperatures (°C) of **3** obtained by liquid-phase and solid-phase synthesis.[a]

m	*n*	Liquid-phase	Solid-phase
2	2	Cr • 244 • N • 299 • I	Cr • 242 • N • 295 • I
2	5	Cr • 208 • SmA • 228 • N • 255 • I	Cr • 208 • SmA • 220 • N • 250 • I
2	8	Cr • 204 • SmA • 238 • N • 244 • I	Cr • 204 • SmA • 244 • N • 248 • I
5	2	Cr • 217 • SmA • 230 • N • 262 • I	Cr • 211 • SmA • 224 • N • 260 • I
5	5	Cr • 194 • SmA • 232 • N • 240 • I	Cr • 197 • SmA • 243 • N • 244 • I
5	8	Cr • 191 • SmC • 204 • SmA • 248 • I	Cr • 189 • SmC • 202 • SmA • 241 • I
8	2	Cr • 202 • SmA • 255 • N • 256 • I	Cr • 195 • SmA • 248 • N • 252 • I
8	5	Cr • 184 • SmA • 243 • I	Cr • 182 • SmA • 242 • I
8	8	Cr • 180 • SmC • 188 • SmA • 237 • I	Cr • 179 • SmC • 188 • SmA • 234 • I

Note: [a]Cr: crystals, N: nematic phase, SmA: smectic A phase, SmC: smectic C phase, I: isotropic liquid.

almost identical transition temperature to the authentic samples. Since the purity and conversion were sufficient to investigate the thermal behaviour without purification, this simplified work-up, including extraction with solvents, evaporation of the solvents, and purification by chromatography or recrystallisation. In order to further develop combinatorial synthesis in the field of liquid crystals, however, an efficient screening method will be required, as has become well established in the fields of pharmaceutical chemistry, solid-state materials science and catalysis [20]. We have already constructed a simple analytical system using light scattering to assess whether or not liquid crystalline states are present [21].

It can be concluded that solid-phase combinatorial synthesis improves the efficiency of the research process, providing compounds with sufficient purity for the study of thermal properties and avoiding time-consuming purification procedures. These results indicate that solid-phase combinatorial synthesis is a valuable and convenient tool in the synthesis of new types of liquid crystal.

Table 3. Transition temperatures (°C) of two-ring troponoids **4** and **5**.

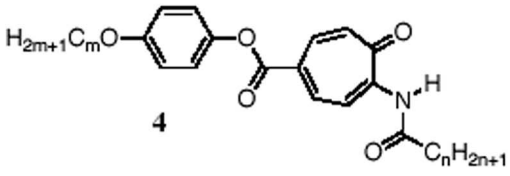
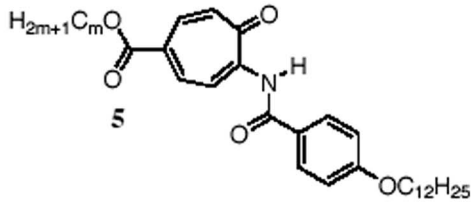
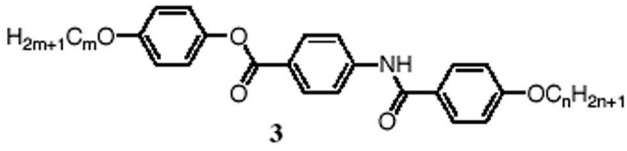
 **4**	 **5**
m=4, *n*=9: Cr • 87 • (SmC • 64) • I *m*=4, *n*=13: Cr • 86 • (SmC • 64) • I *m*=8, *n*=13: Cr • 99 • (SmC • 94) • I *m*=12, *n*=13: Cr • 85 • (SmC • 64) • I ( ) indicates monotropic transition.	*m*=8: Cr • 84 • SmC • 89 • I *m*=14: Cr • 77 • SmC • 88 • I

Table 4. Transition temperatures (°C) of three-ring benzenoid **3** and troponoid **6**.



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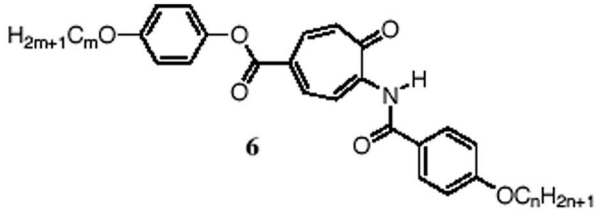


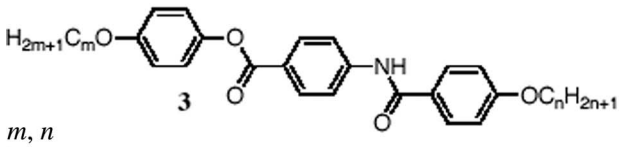
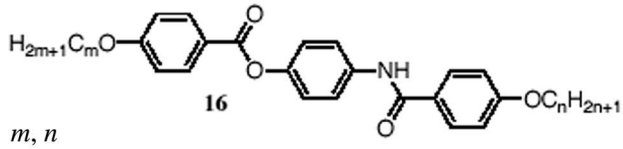
6

m	*n*	**3**	*m*	*n*	**6**
4	4	Cr • 200 • SmA • 237 • N • 250 • I	4	4	Cr • 111 • SmC • 123 • N • 149 • I
4	8	Cr • 189 • SmA • 246 • I	4	8	Cr • 101 • N • 142 • I
4	10	Cr • 183 • SmC • 201 • SmA • 240 • I	4	12	Cr • 93 • SmC • 120 • N • 122 • I
8	4	Cr • 176 • SmA • 244 • I	8	4	Cr • 124 • (SmC • 114 •) N • 142 • I
8	8	Cr • 179 • SmC • 188 • SmA • 234 • I	8	8	Cr • 85 • SmC • 110 • N • 133 • I
8	10	Cr • 179 • SmC • 218 • SmA • 233 • I	8	12	Cr • 100 • SmC • 134 • N • 151 • I
10	4	Cr • 176 • SmA • 240 • I	10	4	
10	8	Cr • 177 • SmC • 191 • SmA • 236 • I	10	8	Cr • 108 • SmC • 162 • N • 168 • I
10	10	Cr • 175 • SmC • 216 • SmA • 231 • I	10	12	Cr • 107 • SmC • 162 • N • 166 • I

4. Experimental

All commercially available chemicals were used without further purification. The BAL was purchased from Mimotopes Pty Ltd (Victoria, Australia). The conversion and purity of products used in solid-phase synthesis were determined by HPLC (Hewlett–Packard series 1100, GL Science Inc, Inertsil ODS–3, 4.6 × 75 mm^2, 0.1% HCO_2H/H_2O and 0.1% HCO_2H/CH_3CN) with the peak area monitored at 254 nm by UV spectroscopy. The stationary phases for column chromatography were Wako gel C–300 and alumina (Kishida Chemical Co Ltd) and the eluent was chloroform. A mixture of ethyl acetate and hexane was used for recrystallisation. Elemental analysis was carried out at Kyushu University. NMR spectra were measured on JEOL LA 400 spectrometer; the chemical

Table 5. Comparison of transition temperatures (°C) of **3** and **16**.

m, *n*	 **3**	*m*, *n*	 **16**
1	Cr • 229 • N • 316 • I	1	Cr • 255 • N • 303 • I[a]
4	Cr • 200 • SmA • 237 • N • 250 • I	4	Cr • 229 • N • 254 • I[a]
6	Cr • 188 • SmA • 242 • I	6	Cr • 190 • SmC • 198 • N • 230 • I
8	Cr • 179 • SmC • 188 • SmA • 234 • I	8	Cr • 185 • SmC • 220 • N • 222 • I
10	Cr • 175 • SmC • 216 • SmA • 231 • I	10	Cr • 175 • SmC • 220 • I

Note: [a]Reference [13].

shifts are expressed in δ units. Mass spectra measurement conditions were Electrospray–TOF MS on a Mariner TK 3500 biospectrometer. Transition temperatures were measured using a differential scanning calorimeter (Seiko DSC 200) at a scanning rate of 5°C min^{-1}, and the mesomorphic phase was observed by means of a polarising microscope (Olympus BHSP BH–2) equipped with hot-stage (Linkam TH–600RMS). X-ray powder diffraction measurements were carried out using the Rigaku Rint 2100 system using Ni-filtered Cu–K radiation at a range of temperatures, controlled with a Linkam HFS–91 hot-stage.

4.1 Loading of 4-iodoaniline on BAL

Six pieces of BAL (D–series lantern, 35 μmol), previously swollen in dimethyl formamide (DMF) for 20 min, were placed in a bottle to enable reaction with 4-iodoaniline (**7**; 329 mg, 1.5 mmol), and 0.05 M $NaBH_3CN$ (9.43 mg, 0.15 mmol) in DMF (3 ml) containing 1% acetic acid, at 60°C over 34 h. After the solution had been removed by decantation, lanterns, **8**, were washed with DMF (5 min × 3) and dichloromethane (5 min × 3), and dried under reduced pressure. After a piece of lantern **8** was reacted in dichloromethane containing 20% TFA for 1 h, the solvent was removed to yield 4-iodoaniline. The loading quantity of **7** on lantern **8** was determined as 41% at 99% purity. The conversion is shown in the table in Scheme 3.

4.2 Solid-phase acylation

Four pieces of lantern **8**, previously swollen in DMF for 20 min, were placed in a vital bottle to react with 0.3 M hexanoyl chloride (0.9 mmol) in a mixture (3 ml) of dichloromethane containing 0.5 M triethylamine (209 μl, 1.5 mmol) at room temperature for 17 h. After the solution had been removed by decantation, lanterns **9** ($n = 5$) were washed in turn with dichloromethane (3 min × 5), THF (5 min × 2, overnight × 1), a 1 : 1 mixture of acetic acid and water (5 min × 3, at 60°C), a 1 : 9 mixture of triethylamine and THF (5 min × 3), a 1 : 1 mixture of THF and water (5 min × 3), THF (5 min × 3), toluene (5 min × 3) and dichloromethane (5 min × 3), and dried under reduced pressure. After a piece of lantern **9** ($n = 5$) was reacted in dichloromethane containing 20% TFA for 1 h at room temperature, the solvent was removed to yield 4-iodo-1-hexanoylaniline (**14**, $n = 5$). The other lanterns **9** ($n = 9$ and 13) were synthesised similarly. The loading and purity were determined and are summarised in the table in Scheme 4.

4.3 Solid-phase benzoylation

Eleven pieces of lantern **8**, previously swollen in DMF for 20 min, were placed in a vital bottle to react with 0.3 M 4-methoxybenzoyl chloride (2.1 mmol) in a mixture (7 ml) of dichloromethane and 0.5 M triethylamine (488 μl, 3.5 mmol) at room temperature for 17 h. After similar work-up to that for lantern **10** ($n = 1$), 4-iodo-1-(4-methoxybenzoyl)aniline (**15**, $n = 1$) was obtained. The other lanterns **10** ($n = 2$–10) were synthesised similarly. The loading and purity were determined and are summarised in the table in Scheme 4.

4.4 Solid-phase carbonylation on solid support

4.4.1 4-Alkoxyphenyl 4-(alkylcarbonylamino) benzoates **(1)**

Three pieces of lantern **9** ($n = 2$), previously swollen in DMF for 20 min, were separately placed in three test tubes. Each test tube contained a solution in DMF (4 ml) of 0.5 M one of the 4-alkoxyphenols ($m = 4$, 8 or

12) (2.0 mmol), 0.5 M triethylamine (279 μl, 2.0 mmol) and 0.01 M tetrakis(triphenyphosphine)palladium(0) (46.3 mg, 0.04 mmol). The three test tubes were placed in an autoclave under carbon monoxide (10 atm) and heated at 60°C for 75 h. After a similar work-up to that described above, compounds **1** ($m = 4$, $n = 2$; $m = 8$, $n = 2$; $m = 12$, $n = 2$) were obtained. The other compounds **1** ($m = 8$, $n = 2$, 5 or 8; $m = 12$, $n = 2$, 5 or 8) were synthesised similarly. The conversion and purity were determined and summarised in Scheme 5.

4.4.2 Alkyl 4-(4-alkoxybenzoylamino)benzoates **(2)**

Similarly, alkyl 4-(4-alkoxybenzoylamino)benzoates (**2**) were obtained from lantern **10** ($n = 2$, 5 or 8). The conversion and purity are summarised in Scheme 5.

4.4.3 Synthesis of 4-alkoxyphenyl 4-(4-alkoxybenzoylamino)benzoates **(3)**

Ten pieces of lantern **10** ($n = 1$), previously swollen in DMF for 20 min, were placed separately in test tubes. Each test tube contained a DMF solution (8 ml) of 0.5 M, one of the 4-alkoxyphenols ($n = 1$–10, 4.0 mmol), 0.5 M triethylamine (557 μl, 4.0 mmol), and 0.01 M tetrakis(triphenyphosphine)palladium(0) (92.5 mg, 0.08 mmol). The ten test tubes were placed in an autoclave under carbon monoxide (10 atm) and heated at 60°C for 75 h. After the usual work-up, each piece of lantern **13** was reacted individually in dichloromethane containing 20% TFA for 1 h, and the solvent removed to give the final product. The other 4-alkoxyphenyl 4-(4-alkoxybenzoylamino)benzoates (**3**) were similarly synthesised. The purity of **3** is summarised in Scheme 6.

4.5 Liquid-phase synthesis of 4-iodo-1-(4-alkoxybenzoyl)anilines **(15)**

4-Pentyloxybenzoyl chloride (621 mg, 2.74 mmol) was added to a pyridine solution (3 ml) of 4-iodoaniline (400 mg, 1.83 mmol) in the presence of a catalytic amount of 4-dimethylaminopyridine, and the solution was stirred at room temperature for 2 h. After 2 M HCl solution had been added to the mixture in an ice bath, the reaction mixture was extracted with ethyl acetate. The organic layer was washed in turn with 2 M HCl, a saturated solution of sodium bicarbonate and a saturated solution of NaCl, before drying over magnesium sulphate. After removing the solvent the residue was recrystallised to give compound **15** ($n = 5$):

Colourless crystals, m.p. 221°C, yield 639 mg (86%).
^{1}H NMR ($CDCl_3$) δ 0.94 (3H, t, $J = 7.5$ Hz), 1.43 (4H, m), 1.82 (2H, quin, $J = 7.5$ Hz), 4.02 (2H, t, $J = 7.5$ Hz), 6.96 (2H, d, $J = 8.6$ Hz), 7.43 (2H, d, $J = 8.6$ Hz), 7.66 (2H, d, $J = 8.6$ Hz), 7.68 (1H, br s), 7.81 (2H, d, $J = 8.6$ Hz).
^{13}C NMR (DMSO–d_6) δ 13.89, 21.85, 27.63, 28.24, 67.71, 86.90, 114.01 (2C), 122.36 (2C), 126.45, 129.59 (2C), 137.15 (2C), 139.22, 161.42, 164.91.
Elemental analysis. Found: C, 52.91; H, 4.90; N, 3.41%; calculated for $C_{18}H_{20}INO_2$: C, 52.83; H, 4.93; N, 3.42%.

Compound **15** ($n = 2$):
Colourless crystals, m.p. 248°C, yield 89%.
Elemental analysis. Found: C, 49.15; H, 3.82; N, 3.83%; calculated for $C_{15}H_{14}INO_2$: C, 49.07; H, 3.84; N, 3.82%.

Compound **15** ($n = 8$):
Colourless crystals, m.p. 200°C, yield 83%.
Elemental analysis. Found: C, 56.00; H, 5.81; N, 3.07%; calculated for $C_{21}H_{26}INO_2$: C, 55.88; H, 5.81; N, 3.10%.

4.6 Liquid-phase synthesis of 4-alkoxyphenyl 4-(4-alkoxybenzoylamino)benzoates

4.6.1 4-Ethoxyphenyl 4-(4-ethoxybenzoylamino) benzoate, **3** *(m = n = 2)*

A solution in 5 ml DMF of 4-iodo-1-(4-ethoxybenzoyl)aniline, **15** ($n = 2$) (100 mg, 0.272 mmol), 4-ethoxyphenol (45.2 mg, 0.33 mmol), tetrakis (triphenyphosphine)palladium(0) (31.5 mg, 0.027 mmol) and triethylamine (55 mg, 0.54 mmol) was placed in an autoclave under carbon monoxide (5 atm) and heated at 60°C for 75 h. After 2 M hydrochloric acid was added to the reaction mixture, the resulting precipitate was filtered off. The precipitate was chromatographed on a silica gel and alumina column to give compound **3** ($m = n = 2$):
Colourless crystals, m.p. 244°C, yield 67 mg (61%).
^{1}H NMR (DMSO–d_6) δ 1.34 (3H, t, $J = 7.0$ Hz), 1.37 (3H, t, $J = 7.0$ Hz), 4.04 (2H, q, $J = 7.0$ Hz), 4.13 (2H, q, $J = 7.0$ Hz), 6.98 (2H, d, $J = 8.9$ Hz), 7.07 (2H, d, $J = 8.9$ Hz), 7.18 (2H, d, $J = 8.9$ Hz), 7.98 (2H, d, $J = 8.9$ Hz), 8.01 (2H, d, $J = 8.9$ Hz), 8.10 (2H, d, $J = 8.9$ Hz), 10.46 (1H, s).
Elemental analysis. Found: C, 70.25; H, 5.70; N, 3.47%; calculated for $C_{24}H_{23}NO_5$: C, 71.10; H, 5.72; N, 3.45%.

Compound **3** ($m = 2$, $n = 5$):
Colourless crystals, m.p. 208°C, yield 92%.
Elemental analysis. Found: C, 72.10; H, 6.48; N, 3.10%; calculated for $C_{27}H_{29}NO_5$: C, 72.46; H, 6.53; N, 3.13%.

Compound **3** ($m = 2$, $n = 8$):
Colourless crystals, m.p. 204°C, yield 96%.
Elemental analysis. Found: C, 73.38; H, 7.20; N, 2.95%; calculated for $C_{30}H_{35}NO_5$: C, 73.60; H, 7.21; N, 2.86%.

Compound **3** ($m = 5$, $n = 2$):
Colourless crystals, m.p. 217°C, yield 93%.
Elemental analysis. Found: C, 72.19; H, 6.51; N, 3.15%; calculated for $C_{27}H_{29}NO_5$: C, 72.46; H, 6.53; N, 3.13%.

Compound **3** ($m = n = 5$):
Colourless crystals, m.p. 194°C, yield 94%.
Elemental analysis. Found: C, 73.44; H, 7.19; N, 2.90%; calculated for $C_{30}H_{35}NO_5$: C, 73.59; H, 7.21; N, 2.86%.

Compound **3** ($m = 5$, $n = 8$):
Colourless crystals, m.p. 191°C, yield 95%.
Elemental analysis. Found: C, 74.41; H, 7.74; N, 2.64%; calculated for $C_{33}H_{41}NO_5$: C, 74.55; H, 7.77; N, 2.63%.

Compound **3** ($m = 8$, $n = 2$):
Colourless crystals, m.p. 202°C, yield 96%.
Elemental analysis. Found: C, 73.41; H, 7.19; N, 2.92%; calculated for $C_{30}H_{35}NO_5$: C, 73.60; H, 7.21; N, 2.86%.

Compound **3** ($m = 8$, $n = 5$):
Colourless crystals, m.p. 184°C, yield 95%.
Elemental analysis. Found: C, 74.46; H, 7.76; N, 2.70%; calculated for $C_{33}H_{41}NO_5$: C, 74.55; H, 7.77; N, 2.63%.

Compound **3** ($m = n = 8$):
Colourless crystals, m.p. 180°C, yield 95%.
Elemental analysis. Found: C, 75.26; H, 8.23; N, 2.50%; calculated for $C_{36}H_{47}NO_5$: C, 75.36; H, 8.26; N, 2.44%.

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