

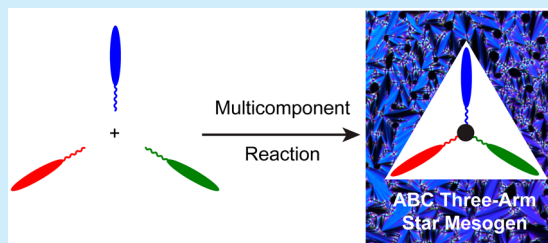
Efficient Syntheses of Star-Branched, Multifunctional Mesogens

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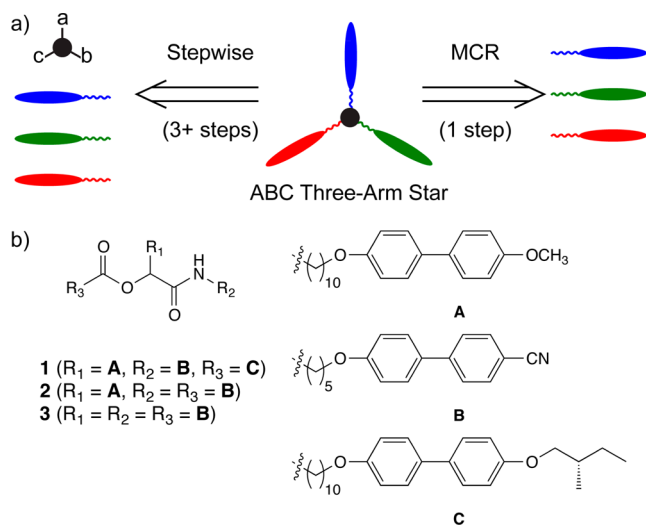
S Supporting Information

ABSTRACT: Star-branched molecular architectures lend themselves to convergent synthesis strategies for creating materials that combine three or more functional modalities, but these approaches require a core moiety with several reactive groups that are orthogonal to one another. The direct synthesis of three-arm, star-branched mesogens has been investigated via the Passerini three-component reaction to demonstrate how multicomponent reactions circumvent the need to identify and synthesize specialized branched core molecules.



Multicomponent reactions (MCRs) enable rapid access to enormous structural diversity by assembling three or more different reactants in a single chemical transformation.¹ Convergent synthesis strategies that culminate in an MCR minimize the number of chemical operations that are performed on valuable, functional moieties (Scheme 1a). Such strategies

Scheme 1. Multifunctional ABC Three-Arm, Star-Branched Compounds



also help to mitigate functional group incompatibilities during a synthesis campaign. A hallmark of MCRs that has been exploited to produce combinatorial libraries of compounds with potential biological activities is their modularity.¹ Each component in these reactions offers a degree of freedom for introducing structural and functional variability. The combination of efficiency and modularity of MCRs is well suited for the synthesis of multifunctional materials (Scheme 1a), where the properties of different functional subunits are combined into a single molecule.²

Identifying a suitable core through which the arms of the star-branched molecule are joined is a critical challenge when different functional modalities are to be combined.³ Star-branched molecules with identical arms have been synthesized for multivalent display of carbohydrates,⁴ peptides and peptidomimetics,⁵ supramolecular host–guest systems,⁶ and liquid crystal mesogens.⁷ Successful syntheses of nonsymmetric star-branched materials have relied heavily on strategies to desymmetrize core molecules with equivalent reactive functional groups.³ An ABC three-arm star in which all three arms are different from each other has C_1 symmetry that matches the symmetry of a Passerini reaction⁸ product (e.g., **1** in Scheme 1b).⁹ The Passerini reaction can also be applied to the synthesis of star compounds in which two arms (AB_2) or all three arms are identical, such as **2** and **3** (Scheme 1b), respectively. Herein, the Passerini reaction⁸ serves as a representative MCR for synthesizing star-branched mesogens of varied composition. Other MCRs in which three or more different components are combined would yield similarly novel and complex star-branched, multifunctional materials.

Thermotropic mesogens exist, over a certain temperature range, in a liquid phase that retains some of the positional or orientational order that is found in crystalline solids.¹⁰ Liquid crystalline mesophases composed of thermotropic mesogens have made a profound impact with respect to display technologies.¹¹ The increased molecular weight of the star-branched mesogen compared to the monomeric precursor helps to stabilize the liquid crystalline mesophase,^{12,13} and upon cooling, symmetric star-branched mesogens tend to form stable glassy phases that retain the molecular organization of the liquid crystal phase.^{12b,14} The presence of anisotropic molecular organization in the fluid and glassy states of these materials is promising for bottom-up fabrication of nanostructured materials.^{7,15} Interest in nonsymmetric star-branched mesogens, wherein one or more arms is different from the others, has

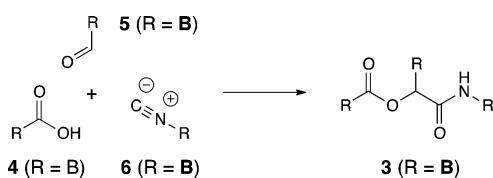
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focused on the prospect that combinations of different mesogenic subunits will lead to unique polymorphism or novel mesophases.^{16–18}

A direct synthesis of ABC three-arm star-branched mesogens from mesogen precursors has yet to be reported. Lehmann and Jahr developed a four-step synthesis of a desymmetrized and orthogonally protected derivative of phloroglucinol¹⁹ that has been used in the synthesis of the largest series of ABC three-arm star-branched mesogens.¹⁷ Assembling star-branched mesogens directly from mesogen components circumvents the challenges of synthesizing and/or functionalizing a nonsymmetric core. Lai and co-workers reported the one-pot synthesis of 2,4,6-trisubstituted pyrimidine-based AB₂ star-branched liquid crystals directly from promesogen precursors.²⁰ The syntheses of 1–3 via the Passerini reaction highlight the efficiency and versatility of the MCR strategy compared to these previous reports. Because compounds 1–3 are the first examples of thermotropic liquid crystals based on the flexible and nonsymmetric α -acyloxyamide core, it is of interest to determine whether this motif supports mesomorphism. We were also intrigued as to whether mesomorphism would be present in the ABC star with calamitic mesogens (1).

To explore a convergent synthesis of three-arm star-branched mesogens from monomeric precursors via an MCR, we focused on the Passerini reaction of 4–6 (Table 1). Carboxylic acid 4 has

Table 1. Evaluation of Reaction Conditions



entry	conditions	yield (%)
1	THF, rt, 7 d ^a	54
2	THF, reflux, 7 h ^a	67
3	DCE, reflux, 7 h ^a	67
4	neat, 110 °C, 7 h ^b	75

^aThe heterogeneous reaction was performed with a nominal [6]₀ = 0.53 M and [4]₀: [5]₀: [6]₀ = 1:1:1. ^b[6]₀ = 1.12 M and [4]₀: [5]₀: [6]₀ = 1:1:1.

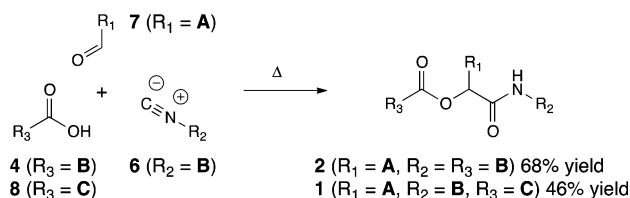
been used in syntheses of star-branched²¹ and dendritic liquid crystals,²² and aldehyde 5 has been used as a mesogen for side-chain liquid crystalline polymers.²³ Each was prepared in two steps from commercially available materials. We designed isocyanide 6 to have the same mesogen and flexible linker as 4 and 5, and 6 was prepared in five steps. Because compound 4 has limited solubility in a range of organic solvents,²⁴ we were pleased to find that Passerini reactions of 4 were successful under a range of heterogeneous and solvent-free conditions.^{25,26} Good yields of 3 were obtained from heterogeneous reactions at reflux in THF or 1,2-dichloroethane (DCE). Our best results were obtained when the reaction was performed without any solvent and at a temperature where compounds 3–6 were in their isotropic liquid phases. Unlike the reactions in THF and DCE, the solvent-free Passerini reaction remained homogeneous throughout the experiment. The convenience of performing reactions in the melt motivated us to apply these conditions to the synthesis of three-arm, star-branched compounds 1 and 2.

The Passerini reaction offers tremendous flexibility with respect to the diversity of mesogens that can be incorporated in

the star-branched compounds. Isocyanide and aldehyde functional groups are rare among mesogens,^{10,11} and carboxylic acid containing mesogens are generally used in cases where specialized supramolecular interactions are desired.²⁷ Thus, the functional groups required for the Passerini reaction are largely orthogonal to those found in thermotropic mesogens. Furthermore, the Passerini reaction has been shown to be compatible with a wide range of functional groups found in mesogens, including azo compounds,⁸ electron-rich and -poor aromatics and heteroaromatics (especially nitroaromatics),^{25,28,29} halogens,^{25,28–30} and sulfones. Imines (and their precursors) are notable exceptions, as these participate in the Ugi reaction³¹ with carboxylic acids and isocyanides. The mesogenic groups A, B, and C (Scheme 1b) were, therefore, chosen for convenience rather than concern for the substrate scope of the Passerini reaction.

We exploited the modularity of the Passerini reaction to prepare the AB₂ (2) and ABC (1) three-arm, star-branched mesogens directly from mesogen precursors. Aldehyde 7 was prepared in three steps. Substituting 7 for 5 in a Passerini reaction with 4 and 6 provided 2 in 68% yield after heating the neat reaction mixture for 2 h at 110 °C (Scheme 2), a temperature that

Scheme 2. Synthesis of AB₂ and ABC Three-Arm, Star-Branched Mesogens



is below the isotropization temperature of the product (vide infra). When the reaction was heated above the isotropization temperature of 2, we isolated the product in lower overall yield (e.g., 58% yield after 7 h at 130 °C) due to side-reaction products that were difficult to separate by flash column chromatography. Carboxylic acid 8 was prepared in five steps from (*S*)-amyl alcohol. We then replaced carboxylic acid 4 with 8 in a Passerini reaction with 6 and 7. The reaction was performed for 7 h at 150 °C because the product (1) has such a high melting temperature (vide infra). The ABC three-arm, star-branched compound 1 was obtained in 46% yield (Scheme 2). Two additional examples of three-arm star compounds are also described in the Supporting Information.³²

Each of the star-branched mesogens (1, 2, and 3) was characterized to assess the mesomorphic properties of these new compounds. Polarizing optical microscopy (POM) experiments were performed on samples of each star-branched mesogen in a temperature-controlled microscopy stage to identify liquid crystalline mesophases by the appearance of a birefringent liquid phase. Indeed, each of the three star-branched mesogens exhibited a mesophase, which demonstrates that the flexibility of the α -acyloxyamide core is tolerated in the mesophase. A fan-shaped focal conic texture was observed from ABC star 1 (Figure 1a), which suggests that this material forms a smectic liquid crystalline phase.³³ Star-branched mesogens 2 (Figure 1b) and 3 (Figure 1c) both exhibit a Schlieren texture that is typical of nematic mesophases.³³ While the low symmetry of the ABC mesogen 1 might be expected to promote the emergence of a nematic phase,¹⁸ which is less ordered than the smectic phase, we believe that the difference in phase behavior between compound

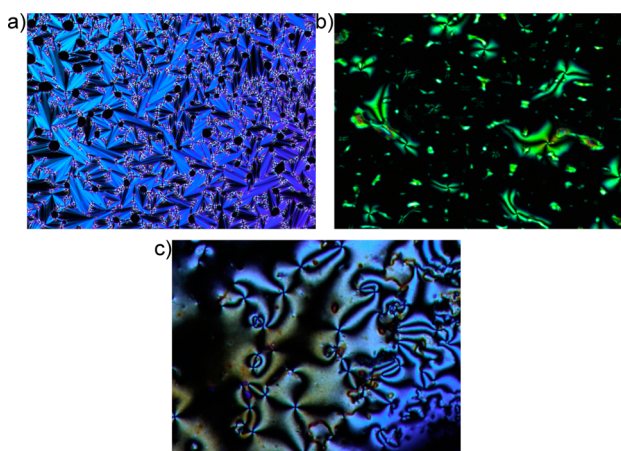


Figure 1. POMs of samples that were slowly cooled from the isotropic liquid phase: (a) **1** (10 \times) at 143 $^{\circ}$ C, (b) **2** (10 \times) at 120 $^{\circ}$ C, and (c) **3** (20 \times) at 109 $^{\circ}$ C.

1 and compounds **2** and **3** is related to the number of long versus short aliphatic chains in the arms. Short spacers restrict ordering of the calamitic mesogens and promote the formation of the nematic phase,³⁴ whereas longer spacers promote smectic ordering by allowing greater conformational freedom to the mesogens.^{12a,21b} Two of the arms in **1** have long alkyl spacers that can promote smectic ordering of the calamitic mesogens, whereas compounds **2** and **3** lack sufficiently flexible arms to allow for such a high degree of order.

Differential scanning calorimetry (DSC) experiments provided temperatures for the corresponding phase transitions and confirmed that the phase behavior is reversible. Representative cooling curves are shown in Figure 2. The temperature range over which the mesophase is present increases in the series of mesogens from the ABC star (**1**) to the AB₂ star (**2**) to the pseudosymmetric star with identical arms (**3**). As the number of arms with long linkers increases both the melting transition temperature and the isotropization temperature increase, but the

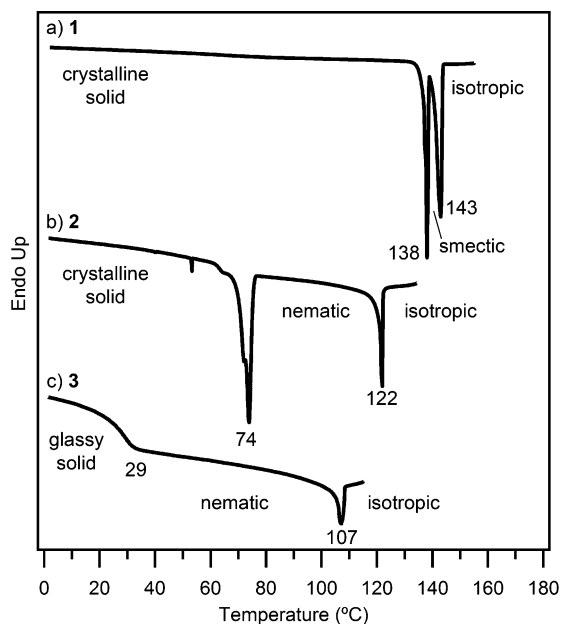


Figure 2. Representative DSC thermograms from the cooling of scans (10 $^{\circ}$ C/min) of (a) **1**, (b) **2**, and (c) **3**.

former increases more rapidly than the latter. While the ABC (**1**) and AB₂ (**2**) star mesogens form crystalline solids upon cooling (Figure 2a,b), star-branched mesogen **3** exhibits characteristics of a symmetric star-branched mesogen^{12,14} such as vitrification upon cooling (Figure 2c). The observed variations in the thermal properties and phase behavior of these star mesogens illustrate the potential to uncover diverse functional properties from libraries of materials prepared via MCRs.³⁵

Multicomponent reactions are a powerful class of transformations with which to explore structural complexity and structural diversity in organic chemistry. The modularity and high degree of convergence achieved through MCRs has fueled combinatorial campaigns aimed at discovering novel compounds with biological activity.¹ Interest in creating innovative organic materials via MCRs has undergone a recent resurgence (e.g., polymers³⁶).² Of particular concern is how MCRs can accelerate studies of multifunctional materials that have been stymied by lengthy and/or low yielding syntheses. ABC Three-arm, star-branched liquid crystals are an example of such materials. We have shown that a three-component reaction, the Passerini reaction, makes it feasible to prepare each permutation of three-arm, star-branched mesogens directly from mesogen precursors. Looking forward, we envision that detailed structure–activity relationships will be established from libraries of star mesogens prepared via MCRs.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, additional experiments, and characterization data. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01388.

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Notes

The authors declare no competing financial interest.

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