

The Concise Synthesis of Unsymmetric Triarylacetonitriles via Pd-Catalyzed Sequential Arylation: A New Synthetic Approach to Tri- and Tetraarylmethanes

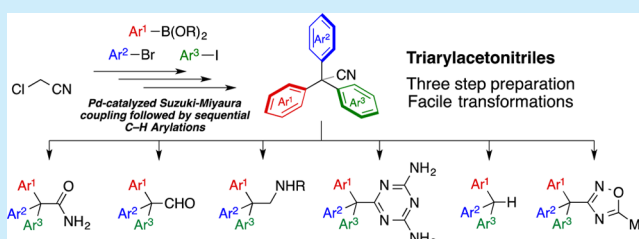
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S Supporting Information

ABSTRACT: The selective synthesis of multiarylated acetonitriles via sequential palladium-catalyzed arylations of chloroacetonitrile is reported. The three aryl groups are installed via a Pd-catalyzed Suzuki–Miyaura cross coupling reaction followed by back-to-back C–H arylations to afford triarylacetonitriles in three steps with no over-arylation at any step. The triarylacetonitrile products can be converted into highly functionalized species including tetraarylmethanes. This new strategy provides rapid access to a variety of unsymmetrical tri- and tetraarylmethane derivatives from simple, readily available starting materials.



The triarylmethane motif is a privileged structure in functional materials¹ including organic dyes,² fluorescent probes for bioimaging,³ and sensors for metal ions.⁴ This substructure is finding new applications in medicinal chemistry including as antitubercular and anticancer agents,⁵ and potassium ion channel blockers,⁶ making versatile, modular routes to these species increasingly important.

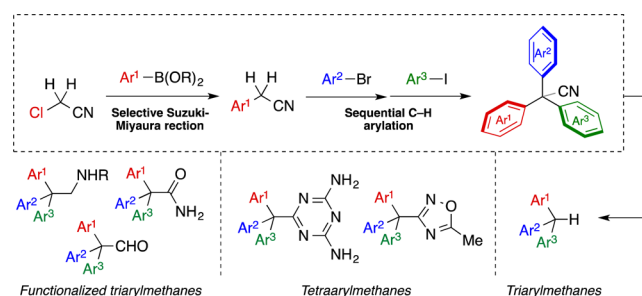
As a part of our program aiming at establishing practical methods for the synthesis of multiply arylated methane derivatives,⁷ we describe herein a straightforward and modular synthesis of privileged triarylacetonitrile structures using chloroacetonitrile as a simple and readily available template.⁸ Three different aryl groups are introduced via an initial Pd-catalyzed Suzuki–Miyaura coupling followed by sequential and selective C–H arylations (Scheme 1). The newly established protocol is very different from classical triarylmethane syntheses, which typically employ the Friedel–Crafts reaction.⁹ This approach is typically restricted to electron-rich aromatics, and

suffers from regioselectivity issues. Our method permits the introduction of three distinct aryl groups without over-arylation, and the reaction is applicable to a range of aromatic substituents including electron-neutral and -poor substrates. Importantly, the nitrile group can be converted into various functional groups, providing access to a number of untapped, densely functionalized molecules of significant interest. For example, unsymmetrical tetraarylmethanes, which are exceptionally difficult to make by other routes, can be synthesized in 1–2 steps from the triarylacetonitrile products. Conditions were also developed to remove the nitrile, providing a viable route to the parent triarylmethanes (Scheme 1).

The transition-metal-catalyzed arylation of acidic sp³ C–H bonds α to electron-withdrawing substituents has proven to be a very effective method for the introduction of one or two aryl groups.¹⁰ Although these reactions are highly effective and have broad scope, the introduction of three aryl groups is unprecedented, likely due to steric constraints in the last arylation.¹¹ Thus, acetonitrile attracted our attention as an interesting potential building block. However, it became quickly obvious that the small size and high activating power of the nitrile was problematic, since diarylation products were always observed,¹² which would be problematic in the synthesis of completely unsymmetrical triarylacetonitriles.¹³

Chloroacetonitrile thus became our preferred starting material in order to avoid C–H arylation at the first step and then rely on steric effects to prevent over-arylation in subsequent C–H functionalizations.¹⁴ For the Suzuki–Miyaura coupling of phenylboronic acid with chloroacetonitrile, we found that

Scheme 1. Synthesis of Triarylacetonitriles and Derivatives via Pd-Catalyzed Sequential Arylation and Transformations



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Table 3. Scope of Third Arylation of 4aa with Iodoarenes 5^a

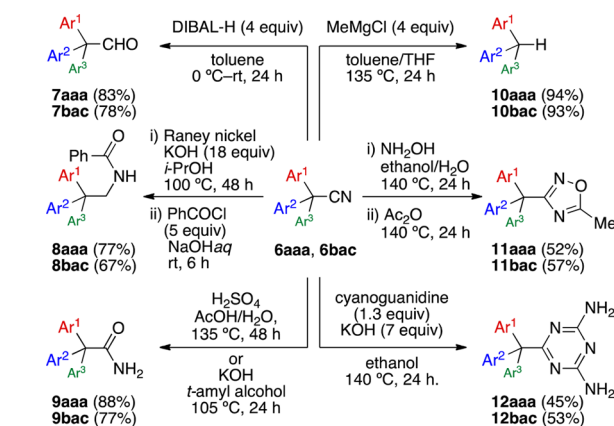
entry	Ar ³	6	yield ^{1b} (%)
1	C ₆ H ₆ (5a)	6aaa	94
2	<i>p</i> -MeC ₆ H ₄ (5b)	6aab	91
3	<i>p</i> -MeOC ₆ H ₄ (5c)	6aac	93
4 ^c	<i>p</i> -Me ₂ NC ₆ H ₄ (5o)	6aao	89
5	<i>p</i> -FC ₆ H ₄ (5d)	6aad	82
6	<i>p</i> -CF ₃ C ₆ H ₄ (5e)	6aae	88
7	<i>o</i> -MeC ₆ H ₄ (5j)	6aaj	73
8	<i>p</i> -MeO ₂ CC ₆ H ₄ (5f)	6aaf	91
9	<i>p</i> -formylC ₆ H ₄ (5m)	6aam	86
10	3-thienyl (5k)	6aak	43
11 ^c	<i>N</i> -methyl-5-indolyl (5n)	6aan	83
12	4-pyridyl (5l)	6aal	77

^aConditions: diphenylacetonitrile 4aa (1 equiv), iodoarene 5 (1.5 equiv), Pd(OAc)₂ (10 mol %), P(*t*-Bu)₃·HBF₄ (30 mol %), Cs₂CO₃ (2 equiv), dioxane (0.5 M), 105 °C, 20 h. ^bIsolated yield. ^cAryl bromide was used as a coupling partner.

Finally, we explored the reactivity of the nitrile functionality. As shown in Scheme 2, treatment of either triphenylacetonitrile (6aaa) or (*p*-methoxyphenyl)(*p*-methylphenyl)phenyl-acetonitrile (6bac) with DIBAL-H afforded the corresponding triarylated acetaldehydes 7 in ca. 80% yields. Reduction with Raney Ni followed by reaction with benzoyl chloride gave amides 8aaa and 8bac in good yields, and acidic or basic hydrolysis gave triarylacetonitriles 9aaa and 9bac in high yields.^{12f}

In addition to these transformations, treatment with MeMgCl at elevated temperature removed the cyano group yielding triarylmethane derivatives 10aaa and 10bac in excellent yields (94% and 93%).¹⁷ This provides an interesting and still concise synthesis of the parent triarylmethanes. Finally the nitrile functional group can be converted into heteroaromatics, resulting in a remarkably concise synthesis of tetraarylmethane derivatives 11aaa, 11bac, 12aaa, and 12bac.

Scheme 2. Transformations of Triarylacetonitriles 6



In summary, we have established a facile and modular synthesis of unsymmetric triarylacetonitriles from chloroacetonitrile through sequential Pd-catalyzed arylation reactions. This method enables the selective introduction of three different aryl groups using readily available arylboronic acids and aryl halides. The triarylacetonitrile products can be transformed into a wide array of compounds including aldehydes, amines, amides, triarylmethanes, and tetraarylmethanes, which are of interest in medicinal chemistry and materials science.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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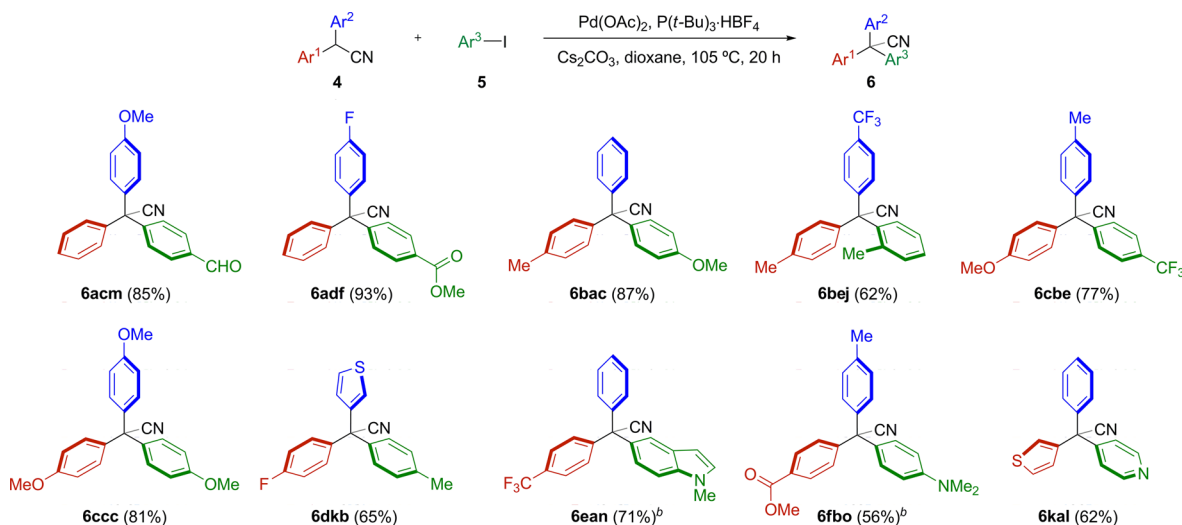


Figure 1. Synthesis of triarylacetonitriles 6. Conditions: diarylacetonitrile 4 (1 equiv), iodoarene 5 (1.5 equiv), Pd(OAc)₂ (10 mol %), P(*t*-Bu)₃·HBF₄ (30 mol %), Cs₂CO₃ (2 equiv), dioxane (0.5 M), 105 °C, 20 h. The number in parentheses is the isolated yield. For 6ean and 6fbo, the corresponding aryl bromide was used as a coupling partner.

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Notes

The authors declare no competing financial interest.

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