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PRACTITIONER PROTOCOL - SYNTHESIS

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An efficient Perkin synthesis of ^{13}C-labelled cinnamic acids from acetic acid as the source of the rare isotope

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This practitioner protocol describes an efficient Perkin synthesis of 1-^{13}C-*p*-alkylcinnamic acids from 1-^{13}C-acetic acid and the benzaldehyde with caesium carbonate and pivalic anhydride as reagents. Our new method employing the nonenolizable pivalic anhydride as the condensation agent avoids the minimum threefold excess of identically labelled carboxylate moieties (in both acid and anhydride) required in a conventional Perkin synthesis to prevent isotope dilution. More generally, this variation of the Perkin synthesis broadens the scope of that classic reaction to valuable carboxylic acid components.

KEYWORDS
cinnamic acids, isotope labelling, Perkin reaction, synthesis

1 | INTRODUCTION

The Perkin reaction[1] is a classic route to cinnamic acids **1** from a carboxylic acid salt **2**, the corresponding anhydride **3**, and an aldehyde **4** (Scheme 1A). In respect to the carboxylic components in **2** and **3**, the atom efficiency in this procedure is poor as—at best—one out of the three carboxylate moieties is transferred to the cinnamic acid **1** while two remain in the product mixture in their free acid form. Thus, unless these acid moieties are recycled—which is hardly an attractive practice in a research lab—the Perkin reaction performed in this conventional fashion is suitable only for readily available low-cost carboxylates.

The parent cinnamic acid is a naturally occurring compound with applications in the perfume industry and pharmaceuticals. It has also been synthesized as a precursor for the enzymatic production of phenylalanine or tyrosine[3] isotope enriched in position 1 by either a Perkin reaction[3a] (from 1-labelled sodium acetate and acetic anhydride with natural isotope abundance) or a Knoevenagel condensation (from 1-labelled malonic acid).[3b] Rare isotope content in the product of the former reaction reached only about 30%. The origin of isotope dilution is illustrated by Scheme 1B: Under the conditions of the Perkin reaction, transesterification between carboxylate and anhydride leads to a reversible exchange among carboxylic residues which is fast relative to the irreversible formation the cinnamic acid. An even more obvious statistic effect will limit the rare isotope content in the second example to 50%. Thus, in the two methods, prevention of isotope dilution would require using anhydrides with labels matching the carboxylate and 1,3-di-labelled malonic acid, respectively.

Faced with the need for a short and efficient synthesis of highly 1-^{13}C enriched cinnamic acids for ^{13}C NMR studies in dilute solutions,[4] we reconsidered the Perkin reaction with a focus on the efficiency of the product

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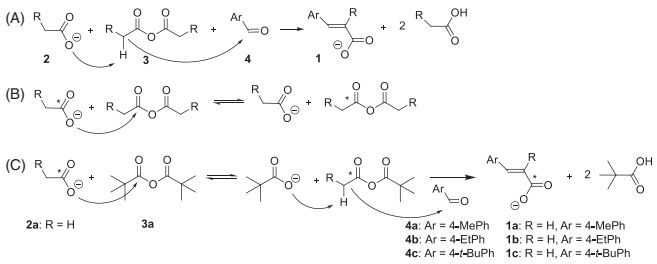

SCHEME 1 A, Typical Perkin reaction between a carboxylic acid salt, the corresponding anhydride and aldehyde leading to cinnamic acids **1** (shown here as the anions initially obtained). B, Transesterification between carboxylate and anhydride. C, Perkin reaction between a carboxylate and a nonenolizable anhydride. In all cases, arrows indicate the succession of electronic shifts formally occurring in the course of the forward reactions. Actual reaction mechanisms may be more complex[2]

integration of valuable carboxylic moieties. The key idea is to employ a carboxylic anhydride consisting of carboxylic groups lacking α protons. Such an auxiliary would not be capable of C—C bond formation with the aldehyde. We hypothesized that if we reacted, as shown in Scheme 1C, a labelled carboxylate (eg, acetate **2a**) with a nonenolizable anhydride (such as pivalic anhydride **3a**) the usual transesterification, eg, to the mixed anhydride (and to acetic anhydride) would occur in situ. Only the labelled acetate residues bearing α protons may then attack the aldehyde **4a** and yield cinnamic acid **1a**.

The irreversibility of the latter reaction would eventually drive the intended conversion of labelled material (from **2a** to **1a**) to completion.

We note that these considerations do not depend on further details of the mechanism[2]: The lack of α protons in the auxiliary anhydride is the prerequisite to exclusive C—C bond formation between the labelled carboxylate and the aldehyde.

2 | EXPERIMENTAL

All starting materials were obtained from commercial suppliers and used as received. Representative procedure for 1-^{13}C-*p*-methylcinnamic acid **1a**:

In a 25-mL three-neck-flask, caesium carbonate (2.7 g, 8.3 mmol) was suspended in diethyl ether (5 mL) and 1-^{13}C-acetic acid **3a** (1.0 mL, 16.6 mmol) was added carefully. When gas evolution had subsided, volatiles were removed under reduced pressure and the residual caesium 1-^{13}C-acetate was further dried at 150°C and 10^{-4} mbar. The flask was flooded with argon, then pivalic anhydride **4a** (6.9 mL, 16.6 mmol) and 4-methylbenzaldehyde **2a** (2 mL, 16.6 mmol) were added, and the reaction mixture was stirred at 180°C for 16 hours. After steam distillation, the residue was dissolved in boiling NaOH solution and precipitated by addition of HCl. The precipitate was filtered off and washed with water before the dissolution/precipitation step was repeated. The product was finally crystallized from dichloromethane and dried under reduced pressure. Yield: 1.54 g (9.5 mmol, 57 %) colorless crystals of **1a**. For the purification of smaller quantities in particular, reversed-phase flash chromatography (C_{18}-bonded silica, gradient of water/methanol in the range from 50% to 80% methanol) is an alternative to the above purification protocol.

^{1}H-NMR (250 MHz, $(CD_3)_2CO$): $\delta = 7.65$ (dd, $J_1(^1H\text{-}^1H)$ = 16 Hz, $J_2(^1H\text{-}^{13}C)$ = 7 Hz, 1H), 7.55 (d, 8 Hz, 2H), 7.25 (d, 8 Hz, 2H), 6.45 (dd, $J_1(^1H\text{-}^1H)$ = 16 Hz, $J_2(^1H\text{-}^{13}C)$ = 3 Hz, 1H), 2.4 ppm (s, 3H); $\{^1H\}^{13}C$ NMR (75 MHz, $(CD_3)_2CO$): δ = 167.09, 144.66, 140.54, 131.85 (d, 7 Hz), 129.55, 128.12, 117.15 (d, 77 Hz), 20.47 ppm.

MS (180 eV, ESI): meas. 162.06; calc. 162.064 $[M\text{-}H]^-$; MS (150 eV, ESI): meas. 164.08 calc. 164.078 $[M + H]^+$, meas. 186.06 calc. 186.061 $[M + Na]^+$.

Using the same procedure, **1b** and **1c** (spectral data in Supporting Information) were obtained from the corresponding aldehydes in very similar yields.

3 | RESULTS AND DISCUSSION

The synthesis of 1-^{13}C-*p*-cinnamic acids **1a-1c** via the new approach to the Perkin synthesis with pivalic anhydride as auxiliary proceeds successfully with a 50% to 60% isolated yield typical for the reaction class suggesting that the partial substitution of acetate by pivalate residues has no detrimental effect on reaction performance. NMR and MS data show that the high degree of 1-^{13}C enrichment present in the acetic acid starting material is preserved in the product. The above protocol includes the formation of the caesium salt[1] from the commercially available free acid so that no additional preparative steps are necessary.

4 | CONCLUSION

We have found a new approach to the Perkin reaction with a nonenolizable anhydride as an auxiliary that allows for an efficient synthesis of isotope labelled cinnamic acids with the carboxylic acid component as the source of the rare isotope. This approach may also prove rewarding in the synthesis of cinnamic acids with (single) extra substituents in position 2, ie, whenever a Perkin reaction with a valuable carboxylic acid component is concerned.

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REFERENCES

1. Koepp E, Vögtle F. Perkin-Synthese mit Cäsiumacetat. *Synthesis*. 1987;1987(02):177-179.
2. Chandrasekhar S, Karri P. Revised mechanism and improved methodology for the Perkin condensation. Resuscitation of the mechanism involving benzal acetate and the improbability of the enolate of acetic anhydride. *Tetrahedron Lett*. 2006;47(13):2249-2251.
3. a Jemielity J, Kańska M, Kański R. Enzymatic synthesis of 1-^{13}C- and 1-^{14}C-L-phenylalanine. *Isotopes Environ Health Stud*. 1998;34(4):335-339. b Augustyniak W, Bukowski J, Jemielity J, Kański R, Kańska M. Enzymatic syntheses of carbon-14 labeled isotopomers of L-phenylalanine. *J Radioanal Nucl Chem*. 2001;247(2):371-374. c Augustyniak W, Kańska R, Kańska M. Synthesis of carbon-14 labeled [1-^{14}C]-, and [2-^{14}C]-L-tyrosine. *J Label Compd Radiopharm*. 2001;44(8):553-560.
4. a Ajami D, Tolstoy PM, Dube H, et al. Encapsulated carboxylic acid dimers with compressed hydrogen bonds. *Angew Chem Int Ed*. 2011;50(2):528-531. b Tolstoy PM, Guo J, Koeppe B, et al. Geometries and Tautomerism of OHN Hydrogen Bonds in Aprotic Solution Probed by H/D Isotope Effects on ^{13}C NMR Chemical Shifts. *J Phys Chem A*. 2010;114(40):10775-10782.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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