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Directed *ortho* Metalation - Cross Coupling Links. Carbamoyl Rendition of the Baker-Venkataraman Rearrangement. Regiospecific Route to Substituted 4-Hydroxycoumarins

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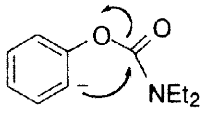
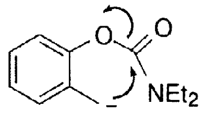
Abstract: A new carbamoyl Baker-Venkataraman rearrangement (**4**) which allows a general synthesis of substituted 4-hydroxycoumarins **8** in 43-82% overall yields is described; the intermediate arylketones **6** are efficiently prepared (59-91% yields) via a Directed *ortho* Metalation - Negishi cross coupling protocol from arylcarbamates **5** and the overall sequence provides a regiospecific anionic Friedel-Crafts complement for the construction of *ortho*-acyl phenols and coumarins. © 1998 Elsevier Science Ltd. All rights reserved.

Previous contributions from our laboratories emanating from the Directed *ortho* Metalaton (D*o*M) strategy[1] include the anionic *ortho*-Fries (**1**),[2] homologous anionic *ortho*-Fries (**2**),[3] and the remote anionic Fries (**3**)[4] rearrangements which offer regiospecific routes, and invariably, mild anionic Friedel-Crafts complements, to polysubstituted aromatics, aryl acetamides and benzofuranones, and polysubstituted biaryls and dibenzo[*b,d*]pyranones respectively. Herein we report a new variant of this anionic aromatic chemistry as a carbamoyl version of the Baker-Venkataraman rearrangement (**4**)[5] for which the requisite *ortho*-acyl arylcarbamates (**6**) are prepared via a regiospecific D*o*M - Negishi cross coupling[6] of arylcarbamates (**5**) with acid chlorides, and which overall allows the rapid construction of substituted 4-hydroxycoumarins (**8**),[7,8] a large and highly diverse class of natural products exhibiting a broad spectrum of bioactivity.[8,9] In the sequel,[10] we demonstrate the application of the D*o*M - Negishi - carbamoyl Baker-Venkataraman strategy to the construction of a putative coumarin natural product and provide its structural revision.



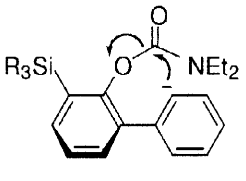
1

Anionic
***ortho*-Fries**



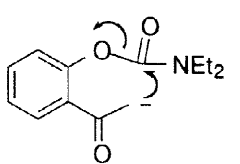
2

Homologous
anionic *ortho*-Fries



3

Remote
anionic Fries

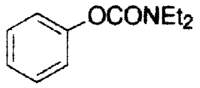
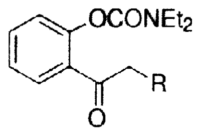
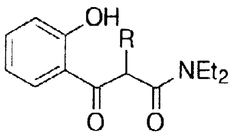
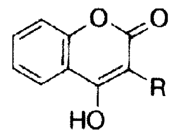
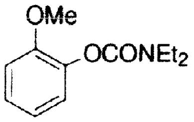
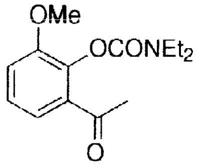
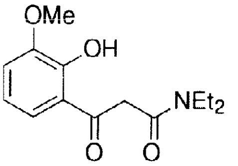
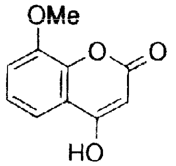
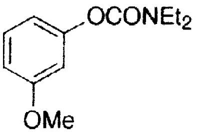
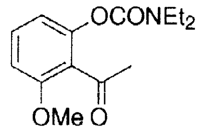
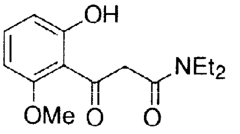
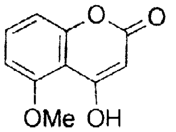
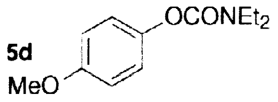
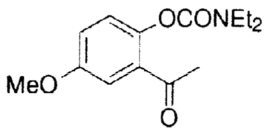
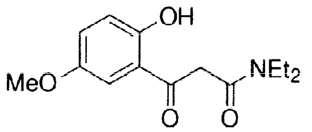
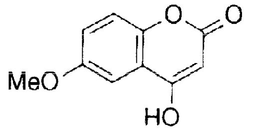
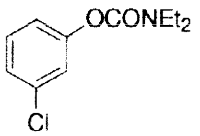
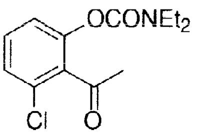
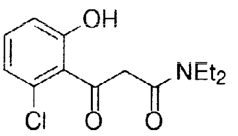
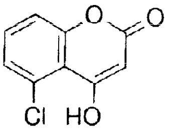
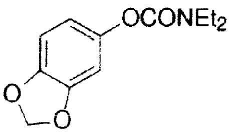
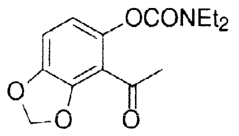
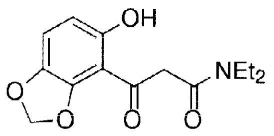
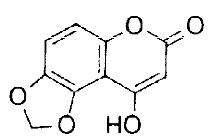
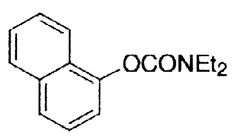
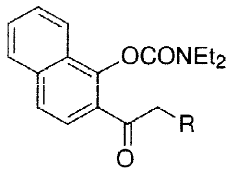
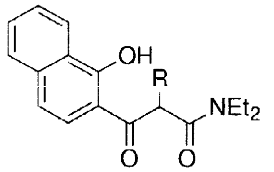
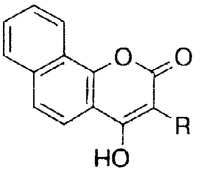


4

Carbamoyl
Baker-Venkataraman

PII: S0040-4039(98)00977-0

Table.[a] **Synthesis of 4-Hydroxycoumarins from Arylcarbamates**

	Arylcarbamate **5**	Arylalkyl ketone **6** (yld, %)	2-Hydroxyaryl acetoacetamide[b] **7** (yld, %) (mp)[c]	4-Hydroxycoumarin **8** (yld, %) (mp)[c]
5a		 **6a**: R = H (96)[d] **6b**: R = Me (95)[d] **6c**: R = Ph (78)	 **7a** (92.5) (85°C) **7b** (97) **7c** (93) (172-173°C)	 **8a** (89) (212-214°C) **8b** (92) (226-227°C subl) **8c** (86) (234-235°C subl)
5b		 **6d** (91)	 **7d** (89) (60-62°C)	 **8d** (89) (253-255°C subl)
5c		 **6e** (67)	 **7e** (95) (98-99°C)	 **8e** (89) (152-153°C)
5d		 **6f** (91)	 **7f** (84) (87-88°C)	 **8f** (85) (272-274°C subl)
5e		 **6g** (79)	 **7g** (84) (137-138°C)	 **8g** (82) (237°C subl)
5f		 **6h** (71)	 **7h** (92) (123-125°C)	 **8h** (86) (subl >250°C)
5g		 **6i**: R = H (86)[d] **6j**: R = Ph (59)	 **7i**: (84) **7j**: (78) (180-181°C)	 **8i**: (79) (284°C dec) **8j**: (95) (263-264°C)

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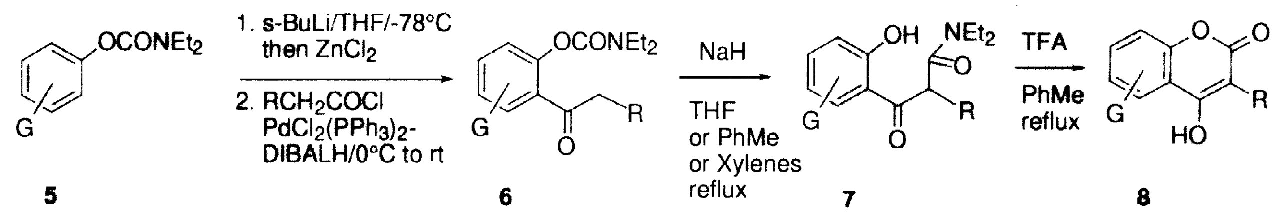
[a] Yields are of chromatographed (silica gel, EtOAc-hexanes eluent) or crystallized/distilled materials. All new compounds show analytical and spectral data in full accord with the given structures. [b] Solvent used for the carbamoyl migration: **7a,b,c,f,g,i,j**: THF; **7d**: PhMe; **7e,h**: Xylenes. [c] Recrystallization solvent: **7a,c,d,e,f,g,h,j**: EtOAc-hexanes; **8a-j**: aq EtOH. [d] Prepared from commercial phenols ($ClCONEt_2/K_2CO_3$/MeCN/reflux).



Selected results of the overall arylcarbamate to 4-hydroxycoumarin conversion, **5** → **8** are presented in the **Table**. With three exceptions (see footnote *d*), *ortho*-acylated arylcarbamates **6** were prepared (59-91% ylds) on 5 mmol scale by metalation of **5**[1] (1.2 equiv s-BuLi/ -78°C/1 h, c 0.5 M/THF) followed by $ZnCl_2$ transmetalation[11] (-78°C) and cross coupling with acid chlorides under conditions described by Negishi[6a] in the presence of 5 mol % of aerially and thermally stable $PdCl_2(PPh_3)_2$ [compare $Pd(PPh_3)_4$] reduced in *situ* by 10 mol % of DIBALH. In the prototype study of the Baker-Venkataraman rearrangement on **6a**, exploration of conditions[12] led to NaH in several solvents (2.5 equiv NaH/THF or PhMe or Xylenes/reflux/1-2 h/c 0.2 M)[13] as the optimal and convenient base affording the 2-hydroxyarylacetamide **7a** in high yield whose conversion into **8a** was effected smoothly with TFA (3 equiv) in refluxing toluene (c 0.25 M)[13]. The absence of side products in the carbamoyl migration reaction even at high (0.2 M) concentration suggests, as demonstrated for the ester Baker-Venkataraman equivalent,[5c] an intramolecular mechanism.

In summary, this work offers a convenient and efficient route to 4-hydroxycoumarins **8**, representing significant and highly diverse class of heterocycles and natural products[7] which exhibit a spectrum of bioactivity[8a,9] with the following preparative advantages: a) the link to D*o*M allows broad scope in aromatic targets[1]; b) the regiospecific installation of the *ortho*-keto function by the Negishi reaction overcomes the non-regioselective and harsh Lewis-acid mediated Fries rearrangement on polysubstituted aromatic frameworks[14a,15]; and c) 3-substituted (alkyl and aryl) coumarins are obtained directly[8c,14b,c,d] by a new carbamoyl Baker-Venkataraman rearrangement **4** whose intramolecularity also provides functional group economy.[10,16]

Acknowledgments. We are grateful to NSERC Canada and Monsanto for support under the Industrial Research Chair and Research Grant programs. AVK (NATO Science Fellowship) and AJMdaS (CNPq Fellowship) are indebted to the named institutions.

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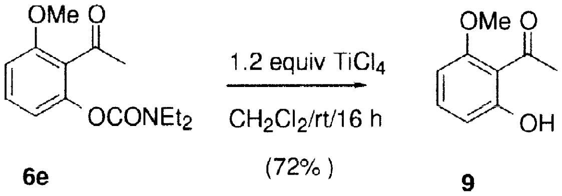
12. LDA/THF/$0^{\circ}C$ (complex mixture); LDA/PhMe/rt (54% yld); BrMgN(i-Pr)$_2$/PhMe/rt → $70^{\circ}C$ (62% yld); K_2CO_3/18-crown-6/PhMe/reflux (no reaction).
13. *Typical Procedure for Carbamoyl Baker-Venkataraman and Cyclization to 4-Hydroxycoumarin Reactions:* To a stirred 0.20 M solution of **6** (for solvent used, see Table, footnote b) was added NaH (2.5 equiv), the reaction mixture was brought to reflux over 1 h, refluxed for an additional 1-2 h, usually accompanied by a massive precipitate/slurry formation and hydrogen evolution. The reaction mixture was cooled in ice-bath, excess NaH was destroyed by slow addition of MeOH followed by addition of NH_4Cl solution. The organic phase was diluted with an equal volume of EtOAc and separated, the aq phase was extracted several times with EtOAc, the combined organic extract was concentrated in vacuum, and the residue was diluted with EtOAc, dried (Na_2SO_4) and purified by column chromatography on silica gel (EtOAc-hexanes eluent) providing **7**.

    To a stirred 0.25 M solution of **7** in PhMe was added TFA (3 equiv) and the reaction mixture was refluxed for 1 h, cooled to rt and concentrated in vacuum. The formed solid residue was recrystallized from aq EtOH providing **8**.
14. a) Review: Martin, R. *Org. Prep. Proc. Int.* **1992**, *24*, 369-435, see esp pp 381, 391, 392, and 409; b) Tabakovic, I.; Tabakovic, K.; Gaon, I. *Org. Prep. Proc. Int.* **1997**, *29*, 223-226; c) Barton, D. H. R.; Donnelly, D. M. X.; Finet, J.-p.; Guiry, P. *J. Chem. Soc. Perkin Trans.* 1 **1992**, *11*, 1365-1375; d) Bohlmann, F.; Steinmeyer, A. *Tetrahedron Lett.* **1986**, *27*, 5359-5362.
15. For example (see ref 14a), Fries rearrangement of 2-OMe and 3-Cl phenol esters affords 5- and 6- acylated products respectively (compare **6d** and **6g**).
16. The DoM - Negishi route to *ortho*-acyl arylcarbamates also serves as an effective route to *ortho*-hydroxyarylacetophenones, e.g. **6e** → **9**, whose value for the synthesis of such complex polysubstituted derivatives as well as natural products is amply recognized, see Martin, R. *Handbook of Hydroxyacetophenones*, Kluwer Academic: Dordrecht. **1997** and Mincheva, Z.; Velkov, J.; Boireau, G.; Barry, J.; Fugier, C. *Synth. Commun.* **1995**, *25*, 149-156.



6e **9**