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Mendeleev Commun., 2021, **31**, 123–124

Mendeleev Communications

An expedient solvent-free C-benzylation of 4-hydroxycoumarin with styrenes

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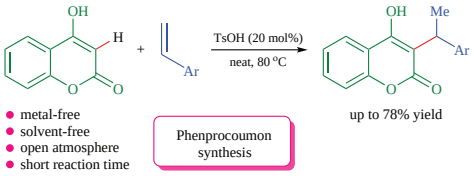
DOI: 10.1016/j.mencom.2021.01.039

An efficient straightforward solvent-free C(3)-benzylation of 4-hydroxycoumarin with styrenes is performed by heating the reactants in the presence of *p*-toluenesulfonic acid. By this procedure, benzylated 4-hydroxycoumarin derivatives which exhibit various biological activities were obtained.



Keywords: 4-hydroxycoumarin, styrene, *p*-toluenesulfonic acid, benzylation, solvent-free.

Coumarin and its derivatives are of a biological and pharmaceutical importance.[1–3] Substituted 4-hydroxycoumarins play a crucial role in the manufacture of various active organic molecules. Among them, 3-alkylated 4-hydroxycoumarins such as warfarin, coumatetralyl, phenprocoumon, difenacoum, brodifacoum, flocoumafen, *etc*. exhibit anti-HIV,[4] antiviral,[5] antifungal,[6] anti-inflammatory,[7] anti-arthritis,[8] antibacterial,[9] antioxidant,[10] anticancer[11] activities. Some of these derivatives are known to be anticoagulants and act as a vitamin K antagonist.[12] On the other hand, 4-hydroxycoumarins serve as good Michael donors in various reactions.[13–14] Several methods have been employed to achieve C_3-alkylation of 4-hydroxycoumarin. Most of them comprise the reaction with benzylic alcohols in the presence of different catalytic reagents like $Bi(OTf)_3$,[15] iodine,[16] $Fe(ClO_4)_3 \cdot xH_2O$,[17] amberlite IR-120,[18] TMSOTf,[19] $FeCl_3 \cdot 6H_2O$,[20] with the processes being carried out in organic solvents. Nitrimines were also employed to synthesize such compounds.[21] Besides, Rueping *et al*. reported C_3-alkylation of 4-hydroxycoumarin with olefins in the presence of bismuth(III) trifluoromethanesulfonate.[15] In this regard, our research was aimed to improve this strategy in view of environmentally acceptable chemicals, catalysts and conditions. During the last five years, we have developed several reaction protocols concerning 4-hydroxycoumarin and organocatalysis that multiply satisfy the environmental issues.[22–25] Herein, we report *p*-toluenesulfonic acid-catalyzed mild and efficient C-benzylation of 4-hydroxycoumarin with styrenes under neat conditions (Scheme 1).†

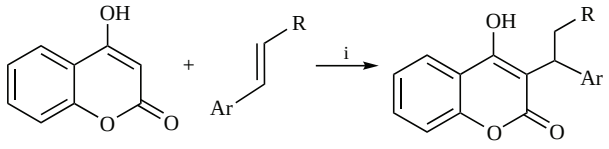
We have initiated our study taking model 4-hydroxycoumarin **1** and styrene **2a** in the presence of 20 mol% of *p*-toluenesulfonic acid (TsOH) when the reactants were stirred in water at 80 °C for 4 h (Table 1, entry 1) to afford 61% of the target product **3a**. Surprisingly, in various organic solvents the yields were even lower (entries 2–6). At that point, we were interested to perform the reaction under neat conditions, which provided a satisfactory yield (78%) of product **3a** (entry 7). Application of other available Brønsted acids rather than TsOH gave nothing of the product (entries 8–12).

Table 1 Optimization of the reaction conditions for model reaction between 4-hydroxycoumarin **1** (1 mmol) and styrene **2a** (1.5 mmol).

Entry	Catalyst (mol%)	Solvent[a]	*T*/°C	*t*/h	Yield of **3a** (%)[b]
1	TsOH (20)	H_2O	80	4	61
2	TsOH (20)	EtOH	80	4	49
3	TsOH (20)	CH_2Cl_2	80	4	28
4	TsOH (20)	1,4-dioxane	80	4	33
5	TsOH (20)	toluene	80	4	16
6	TsOH (20)	MeCN	80	4	21
7	TsOH (20)	neat	80	4	78
8	TFA (20)	neat	80	4	trace
9	HCl (20)	neat	80	4	–
10	HCO_2H (20)	neat	80	4	trace
11	AcOH (20)	neat	80	4	trace
12	$PhCO_2H$ (20)	neat	80	4	trace
13	TsOH (20)	neat	120	4	79
14	TsOH (20)	neat	50	4	37
15	TsOH (20)	neat	80	5	76
16	TsOH (20)	neat	80	3	68
17	TsOH (10)	neat	80	4	45
18	TsOH (30)	neat	80	4	78

[a] 2 ml $mmol^{-1}$. [b] Isolated yield.

† *General procedure for the synthesis of compounds* **3a**–**h**. A mixture of 4-hydroxycoumarin **1** (162 mg, 1 mmol), styrene **2a**–**h** (1.5 mmol) and TsOH (0.034 g, 20 mol%) was stirred at 80 °C for 4–6 h (TLC control). After completion, the reaction mixture was cooled and extracted with ethyl acetate (3 × 15 ml) and water (2 × 10 ml). The organic layer was separated and dried over Na_2SO_4. After evaporation of the solvent under reduced pressure, the crude product was purified by column chromatography on silica gel (60–120 mesh) using light petroleum/ethyl acetate (94:6 to 92:8, v/v) as eluent to afford the pure products **3a**–**h**. For details, see Online Supplementary Materials.



1 **2a–j** **3a–h**

a Ar = Ph, R= H, 78%
b Ar = 2-MeC_6H_4, R= H, 70%
c Ar = 4-MeC_6H_4, R= H, 75%
d Ar = 4-MeOC_6H_4, R= H, 77%
e Ar = 4-ClC_6H_4, R= H, 74%
f Ar = 3-BrC_6H_4, R= H, 72%
g Ar = 4-FC_6H_4, R= H, 73%
h Ar = Ph, R= Me, 68%

2i Ar = 3-$O_2N$$C_6H_4$, R= H, no product
2j Ar = 4-MeOC(O)C_6H_4, R= H, no product

Scheme 1 *Reagents and conditions*: i, **1**/**2** = 1:1.5 (mol/mol), TsOH (20 mol%), neat, 80 °C, 4 h (6 h for **3f**).

Heating plays an important role in this reaction. The yield was not improved noticeably by raising the temperature to 120 °C (entry 13) while a lower yield was obtained on lowering the temperature (entry 14). By prolongation or shortening the reaction time the yield was not raised (entries 15,16). We have observed that 20 mol% of TsOH as the catalyst provided better yield (78%) compared to that (45%) when 10 mol% of TsOH was used (entry 17). Increase in the catalyst loading to 30 mol% did not affect the reaction outcome (entry 18). After considering the above experiments, the optimum conditions were selected to be heating neat mixture of 4-hydroxycoumarin **1** (1 mmol), styrene **2a** (1.5 mmol) and 20 mol% of TsOH at 80 °C for 4 h.

Based on the optimized reaction conditions, we checked the scope and limitations of our reaction procedure (see Scheme 1). Styrenes with alkyl and halogen substituents in arene moiety **2b**–**g** reacted closely to their parent analogue **1a** and gave the corresponding products **3b**–**g** in satisfactory yields. To our delight, we have successfully synthesized phenprocoumon **3h** in 68% yield by coupling β-methylstyrene **2h** with 4-hydroxycoumarin **1**. Unfortunately but not surprisingly, styrenes **2i**,**j** with electron-withdrawing groups in arene core did not react to give desired products **3i**,**j**.

We were interested to prepare anticoagulant drug phenprocoumon **3h** in gram scale range. For this purpose, the reaction between 4-hydroxycoumarin **1** (10 mmol) and β-methylstyrene **2h** (15 mmol) under the optimized conditions afforded 1.7 g (61%) of the desired product **3h**.

In summary, we have developed an efficient procedure for the direct C-benzylation of 4-hydroxycoumarin with styrenes using available, cheap and metal-free catalyst under solvent-free and open-air conditions. By this simple and green procedure, we can synthesize various important 4-hydroxycoumarin derivatives including phenprocoumon in good yields.

A. Majee acknowledges financial support from the CSIR Major Research Project (Ref. no. 02(0383)/19/EMR-II). A. Mukherjee and S. Santra thank the Russian Science Foundation for funding (Grant no. 20-73-10205). G. V. Zyryanov and O. N. Chupakhin are grateful to the Grants Council of the President of the Russian Federation (no. NSh-2700.2020.3) for funding.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2021.01.039.

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Received: 26th August 2020; Com. 20/6296