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Diruthenium(II,II) tetrakis(acetate) as a catalyst of choice for intermolecular insertion of stabilized diazocompounds into O–H bonds

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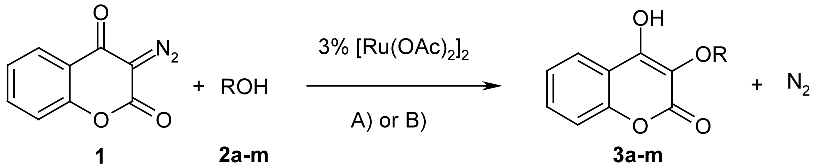
Abstract—In the presence of 3 mol% of $[Ru(OAc)_2]_2$ at 90°C in hexafluorobenzene or alcohols as solvents the highly stabilized diazocoumarin **1** undergoes insertion into the OH bond of alcohols (and phenols) regio- and chemoselectively, affording the corresponding 3-alkoxy-4-hydroxycoumarin in moderate to excellent yields. © 2002 Elsevier Science Ltd. All rights reserved.

The metal-catalyzed decomposition of diazocarbonyl compounds, first observed by Silberrad and Roy[1] in the early 1900s, has attracted much interest in the last two decades. It is one of the most widely employed reactions by virtue of its versatility, including addition to multiple bonds in both inter- and intramolecular fashion, XH insertion and onium ylide formation.[2] In 1950 Casanova and Reichstein[3] observed that heating of a steroidal α-diazo ketone in MeOH in the presence of copper(II) oxide gave the corresponding α-methoxy ketone in excellent yields. Since then, many metal catalysts have been used but none of them has enjoyed as widespread use as dirhodium(II,II) tetrakis(acetate) $[Rh(OAc)_2]_2$, introduced by Teyssié, Hubert and coworkers in 1973.[4] Within this context, a number of metal catalysts [i.e. $Ni(acac)_2$, $2Ti(acac)_3TiCl_6$ complex in the presence of $Cu(acac)_2$, $Sc(OTf)_3$, $AgBF_4$, $Mo_2(OAc)_4$ and $Pd(OAc)_2$] in lieu of $[Rh(OAc)_2]_2$ have been surveyed. The synthetic applications of this reaction have also recently been the subject of Moody's excellent review.[5]

More recently, Michelin reported on the use of Pt(0) and dicationic Pt(II) complexes as efficient catalysts for the insertion of ethyl diazoacetate (EDA) and diazofluorene into the O–H bond of alcohols.[6] Over the past several years we have been developing methods for the synthesis of polyheterocyclic frameworks through the addition of 3-diazobenzopyran-2,4(3*H*)-dione **1** (hereafter called diazocoumarin) to π-systems,[7] a reaction promoted by transition metal complexes. In these studies we became interested in the potential applications of O–H insertion reaction, which, if successful, could provide a straightforward access to 3-alkoxy- and 3-aryloxy-4-hydroxycoumarins (Scheme 1). Many of these compounds that have been isolated from a wide range of natural sources exhibit pharmacologically relevant activity and some of them have proven attractive



Scheme 1.

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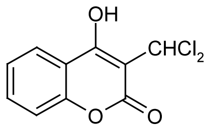
synthetic targets. Our initial attempts to trap the Rh carbenoid from **1** by carrying out the reaction in refluxing MeOH led to messy reactions and incomplete conversion. Such shortcomings could be only partially controlled by the portionwise addition of catalyst (up to 10 mol%). Among all complexes we tried diruthenium(II,II) tetrakis(acetate) $[Ru(OAc)_2]_2$, mimicked $[Rh(OAc)_2]_2$ most closely, being isostructural (D_{4h} symmetry with two vacant coordination sites), although this Ru–Ru doubly-bonded species possesses a $\sigma^2\pi^4\delta^2\pi^{*3}\delta^{*1}$ electronic configuration with two unpaired electrons.[8] Consequently, we decided to use $[Ru(OAc)_2]_2$ to assess its potential as catalyst in the hope of overcoming the O–H insertion problems encountered with $[Rh(OAc)_2]_2$. Gratifyingly, when **1** was exposed to the Ru(II) catalyst (3 mol%) in refluxing MeOH for 2 h, 3-methoxy-4-hydroxycoumarin **3a**[9] was obtained in 95% yield. A number of commercially available Ru-based catalysts were screened [e.g. $Ru_2(OAc)_4Cl$, $Ru(acac)_3$]; however, none were superior to $[Ru(OAc)_2]_2$ in performance. Although numerous Ru complexes have been implicated in catalytic cyclopropanation of alkenes,[10] at the time we began this work there were only two examples in which ruthenium complexes [i.e. $(PPh_3)_3RuCl_2$[11]and $RuCl(\eta^6$-*p*-cymene)$(N\wedge NTs)$ (Demonceau's catalyst)[12]] catalyzed the intermolecular insertion of diazo esters into the O–H bond of alcohols. For the sake of comparison, reaction of **1** (0.2 M in benzene) with MeOH under the conditions originally reported by Sengupta[11] using 3 mol% $(PPh_3)_3RuCl_2$ as the catalyst was much slower and failed to give satisfactory yields of 3-methoxy derivative **3a** (42% after 4 h). The success achieved with the $[Ru(OAc)_2]_2$-catalyzed transformation of **1** in MeOH was extended to a range of alcohols and phenols. With liquid alcohols (Table 1), the reaction was performed simply using an excess of alcohol as solvent (method A) or in the presence of a cosolvent (method B). Working with high boiling or solid alcohols (e.g. geraniol, L-menthol or hexadecanol), a suitable solvent must be both inert and capable of dissolving reasonably high concentrations of the reagents. Dichloromethane, benzene and fluorobenzene have been successfully used as inert solvents in reactions involving metal carbenoids generated from stabilized diazocarbonyls (e.g. EDA); however, the drastic conditions required to react the highly stabilized diazocoumarin **1** (or its metallo carbenoid) might lead to competitive interception of the allegedly inert solvent. In fact, the metallo-carbenoids of **1** have been found to react at reflux with each of the aforementioned solvents, producing varying amounts of byproducts (i.e. **4**, **5** and **6**).[13] The commercially available hexafluorobenzene (bp 82°C) appeared to be a suitable solvent for such reactions since it has been reported that it is completely inert toward bis(carbomethoxy) carbenoid.[14] Optimally, the reaction was carried out heating for 1–5 h at 90°C (oil bath) in a thick-walled screw-capped vial diazocoumarin **1** in hexafluorobenzene in the presence of $[Ru(OAc)_2]_2$ (3 mol%).

Table 1. Intermolecular OH insertion of diazocoumarin **1** with alcohols and phenols

Entry	R	Method[a] (time/h; isolated yield)
a	Me	A (2; 95) ÷ B (1.5; 85)
b	Et	A (2.5; 86) ÷ B (2; 78)
c	*i*-Pr	A (2.5; 75) ÷ B (3; 70)
d	*n*-Bu	B (4; 81)
e	*t*-Bu	A (5; 86) ÷ B (4.5; 63)
f	$PhCH_2$	B (3; 88)
g	*n*-$C_{16}H_{33}$	B (5; 70)
h	L-Menthyl	B (4; 63)
i	Allyl	B (2; 59)
j	$Me_2C{=}CHCH_2$	B (3.5; 47)
k	Geranyl	B (5; 35)
l	$HC{\equiv}C(CH_2)_2$	B (2.5; 89)
m	*p*-Tolyl	B (1.5; 85)

[a] Method A [diazocoumarin (0.25 mmol), ROH (5 mL), catalyst (3.3 mg), reflux, N_2]. Method B [diazocoumarin (0.5 mmol), ROH (2.5 mmol), catalyst (6.6 mg), C_6F_6, 90°C, N_2].



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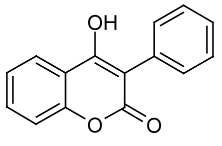

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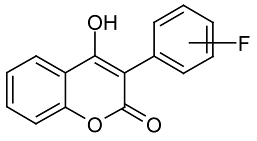

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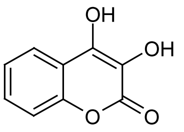

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Excess alcohol (5 equiv.) was necessary for good conversions to the desired 3-alkoxy derivatives **3a**–**m**[15] (method B)[16] in 35–89% range yield. Less satisfactory results were obtained in other perfluorinated solvents (e.g. perfluorodecalin, octafluorotoluene and perfluoro-1,3-dimethylcyclohexane), even at reflux for several hours, owing to the low solubility of **1** in these solvents. The general workup procedure was very simple, requiring only filtration of the crude reaction mixture through a small plug of Florisil® to remove the catalyst prior to concentration by rotary evaporation and purification by silica gel flash chromatography. The procedure was effective for simple primary and secondary alcohols, *t*-BuOH and *p*-cresol. Of particular interest in the case of benzyl alcohol and *p*-cresol, is the overwhelming propensity of the Ru carbenoid to undergo insertion onto O–H bond to give **3f**[15] and **3m**,[15] respectively. No product arising from potential competitive reaction pathways (i.e. aryl C–H insertion or cyclopropanation on benzenoid system) could be found in the crude reaction mixture. Furthermore, we observed that the process works well for alcohols containing an additional functional group such as the double (i.e. allyl alcohol, 3-methyl-2-buten-1-ol and geraniol) or triple C–C bond (i.e. 3-butyn-1-ol). Unfortunately, the 3-prenyl ethers **3j**,**k**[15] either were unstable in the reaction conditions or suffered from subsequent [3,3]-sigmatropic (Claisen) rearrangement,[17] which led to quite modest yields (35–47%).

Taking advantage of the relatively high resistance to acid conditions exhibited by the lactone function in the coumarin derivatives, the 3-*t*-BuO group in compound **3d**[15] was selectively cleaved using trifluoracetic acid (TFA) in CH_2Cl_2 at room temperature for 15 h to provide 3,4-dihydroxycoumarin **7**[15] (81% isolated yield). In the same way, the presence of the 3-*O*-benzyl group in **3i**[15] allowed catalytic transfer hydrogenation (cyclohexene, $Pd(OH)_2$–C in EtOH at reflux, 48 h)[18] to produce **7** in 75% yield. Interestingly, the 3,4-dihydroxycoumarin motif has been described as a useful scaffold to build new potent *aci*-reductones with exciting antioxidant, antiaggregant and antilipidemic properties.[19]

In conclusion, whatever the actual mechanism of heteroatom-hydrogen insertion reaction, diruthenium(II,II) tetrakis(acetate) $[Ru(OAc)_2]_2$ was shown to be a robust and highly effective catalyst for the synthesis of 3-alkoxy- and 3-aryloxy-4-hydroxy coumarins from **1**. The reaction occurs in refluxing neat alcohol (method A) or in hexafluorobenzene as a cosolvent at 90°C (method B); it is simple in execution and workup, leading to products in 35–95% yields. Accordingly, diruthenium(II,II) tetrakis(acetate) stands out as a valuable addition to the arsenal of catalysts that promote the decomposition of strongly stabilized diazocarbonyl compounds. A comparison of current prices also recommends it as a less costly alternative.

Acknowledgements

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8. This unsolvated complex was conveniently synthesized in a two-step one-pot procedure by reduction of commercial $RuCl_3 \cdot xH_2O$ (H_2, 506 kPa, PtO_2, MeOH, 3 h, rt), followed by refluxing (20 h) in the presence of anhydrous NaOAc and drying at 80°C under vacuum (133 Pa) (Lindsay, A. J.; Wilkinson, G.; Motevalli, M.; Hursthouse, M. B. *J. Chem. Soc.*, *Dalton Trans.* **1985**, 2321).
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15. ^1H NMR selected data (400 MHz, $CDCl_3$) for compound **3a**: 1.48 (3H, t, $J=8$ Hz), 7.34 (1H, dt, $J=8$; 2 Hz) 7.35 (1H, dd, $J=8$; 2 Hz), 7.53 (1H, dt, $J=8$; 2 Hz), 7.84 (1H, dd, $J=8$; 2 Hz). Compound **3b**: 1.38 (3H, t, $J=7$ Hz), 4.28 (2H, q, $J=7$ Hz), 7.35 (3H, m), 7.83 (1H, dd, $J=8$; 2 Hz). Compound **3c**: 1.34 (6H, d, $J=7$ Hz), 4.87 (1H, sept, $J=7$ Hz), 7.37 (3H, m), 7.83 (1H, dd, $J=8$; 2 Hz). Compound **3d**: 0.95 (3H, t, $J=7$ Hz), 1.10–2.80 (4H, m), 4.21 (2H, t, $J=7$ Hz), 7.37 (3H, m), 7.83 (1H, dd, $J=8$; 2 Hz). Compound **3e**: 1.48 (9H, s), 7.37 (3H, m), 7.84 (1H, dd, $J=8$; 2 Hz). Compound **3f**: 4.40 (1H, br s, OH), 5.23 (2H, s), 7.30–7.50 (8H, m), 7.69 (1H, dd, $J=8$; 2 Hz). Compound **3g**: 0.88 (3H, t, $J=8$ Hz), 1.10–1.70 (28H, m), 3.64 (2H, t, $J=7$ Hz), 7.37 (3H, m), 7.83 (1H, dd, $J=8$; 2 Hz). Compound **3i**: 4.75 (2H, d, $J=7$ Hz), 5.30 (1H, d, $J=10$ Hz), 5.40 (1H, d, $J=17$ Hz), 6.06 (1H, ddt, $J=17$; 10; 7 Hz), 7.30–7.40 (2H, m), 7.53 (1H, t, $J=7.5$ Hz), 7.82 (1H, t, $J=7.5$ Hz). Compound **3j**: 1.73 (3H, s), 1.75 (3H, s), 4.76 (2H, d, $J=7.5$ Hz), 5.47 (2H, t, $J=7.5$ Hz), 7.06 (1H, br s, OH), 7.40–7.50 (2H, m), 7.51 (1H, dt, $J=8$; 2 Hz), 7.81 (1H, d, $J=8$ Hz). Compound **3k**: 1.61 (3H, s), 1.68 (3H, s), 1.74 (3H, s), 2.00–2.40 (4H, m), 4.54 (2H, d, $J=6.5$ Hz), 5.00–5.20 (1H, m), 5.50 (1H, tq, $J=6.5$; 1.5 Hz), 7.40–7.50 (2H, m), 7.50 (1H, dt, $J=8$; 2 Hz), 7.85 (1H, d, $J=8$ Hz). Compound **3l**: 2.23 (1H, t, $J=2.5$ Hz), 2.56 (2H, dt, $J=6$; 2.5 Hz), 4.33 (2H, t, $J=6$ Hz), 7.30–7.40 (2H, m), 7.55 (1H, dt, $J=8$; 2 Hz), 7.84 (1H, dd, $J=8$; 2 Hz). Compound **3m**: 2.27 (3H, s), 3.70 (1H, br s, OH), 6.70 and 7.05 (4H, AA′XX′ syst), 7.35

(2H, m), 7.53 (1H, dt, $J=8$; 2 Hz), 7.90 (1H, dd, $J=8$, 2 Hz).

16. **Typical procedures (Method A)**: Diazocoumarin **1** (0.25 mmol) was suspended in alcohol **2** (5 mL) in the presence of $[\mathrm{Ru(OAc)_2}]_2$ (3.3 mg) and refluxed under nitrogen for the time indicated in Table 1. The reaction mixture was evaporated under vacuum giving a brown residue that was subjected to preparative TLC (silica gel) to yield **3**. **Method B**: Diazocoumarin **1** (0.50 mmol), alcohol **2** (5 mmol), diruthenium(II,II) tetrakis(acetate) (6.6 mg) were combined in hexafluorobenzene (5 mL) in a dry 10 mL thick-walled resealable Pyrex tube containing a small Teflon®-clad stirring bar. The tube was flushed with nitrogen, sealed with a Teflon® plug and warmed, under stirring, to 90°C (oil bath) for the time indicated in Table 1. The solvent was removed and the residue was filtered through a pad of Florisil® (CH_2Cl_2–EtOAc, 1:1). The solvents were again removed and the dark residue was purified by silica gel flash chromatography (CH_2Cl_2–EtOAc mixture) affording the 3-alkoxy derivative **3**.
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