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Novel chromeno[2,3-*c*]pyrroles synthesized *via* intramolecular rhodium(II) carbene trapping

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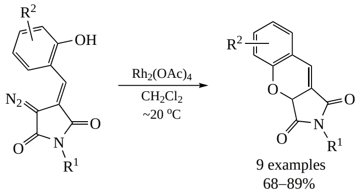
Rhodium(II) carbenes generated from (*E*)-3-diazo-4-(2-hydroxybenzylidene)-1-phenylpyrrolidine-2,5-dione underwent a facile transformation into novel succinimide-fused 2*H*-chromenes, chromeno[2,3-*c*]pyrrole-1,3(2*H*,3a*H*)-diones. The process presumably involves an intramolecular O–H insertion reaction.



Keywords: α-diazo carbonyl compounds, rhodium(II) complexes, intramolecular O–H insertion, 2*H*-chromenes, pyrrolidine-2,5-diones, chromeno[2,3-*c*]pyrroles.

2*H*-Chromenes and dihydro-2*H*-chromenes possess numerous useful biological activities.[1] Illustrative examples of bioactive 2*H*-chromenes include compounds endowed with anti-inflammatory activity,[2] cytotoxic (2*S*)-candenatenin E,[3] tyrosine kinase inhibitory compounds,[4] pesticide hilgartene,[5] antidiabetic serotonin 5-HT_{1A} receptor ligands[6] and potent anti-estrogen acolbifene developed for breast cancer treatment.[7] Dihydro-2*H*-chromene moiety is well represented in various natural products as illustrated by epigallocatechin gallate,[8] procyanidine,[9] myristinine A[10] and aposphearin[11] (for the structures, see Online Supplementary Materials, Figure S1). Numerous strategies for the construction of 2*H*-(dihydro)chromene nucleus have been reported.[12–15] However, considering the clearly privileged character[16] of this heterocyclic core, invention of new synthetic methods to access it, particularly with substitution patterns unattainable by the conventional strategies, is highly desirable.

Recently, we studied a novel type of heterocyclic α-diazo carbonyl compounds, namely, (*E*)-3-arylidene-4-diazopyrrolidine-2,5-diones **1** (Figure 1).[17,18] In particular, we were interested in developing a library of diversely substituted Michael acceptor compounds **2** which were the products of rhodium(II)-catalyzed insertion of the respective metal carbenes into S–H, O–H and N–H bonds of peripheral reagents.[19] While benzylidene-type substrates **1** proved rather effective and gave good to high yields of regiochemically unequivocal adducts **2**, analogous 2-pyridylmethylene substrates **3** did not provide any X–H insertion product **4** at all. Instead, cyclization into indolizines **5** was the predominant (and quite high-yielding) process (see Figure 1).[20] We reasoned that if a rhodium(II) carbene was generated from a diazo substrate bearing a nearby 2-hydroxybenzylidene group, formation of 2*H*-chromene could be highly likely. Herein, we report on the realization of the latter strategy.

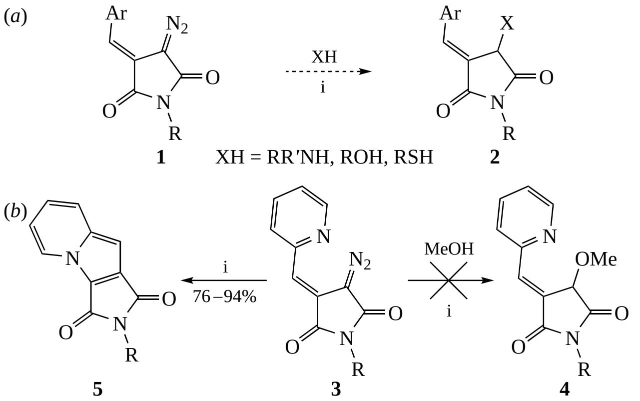
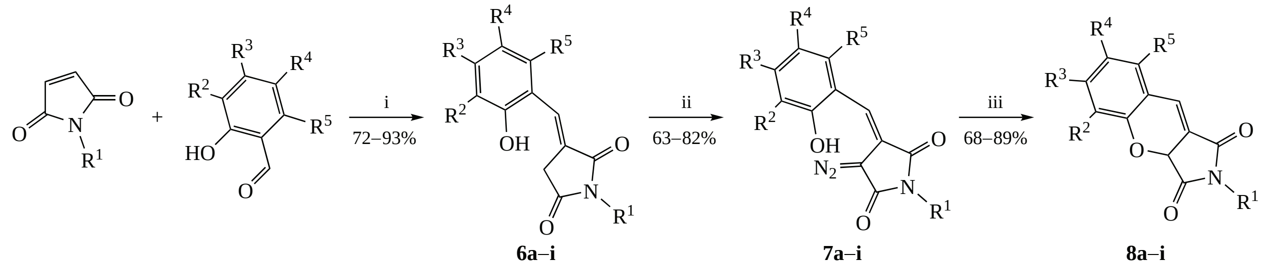


Figure 1 Expected (*a*) and unexpected (*b*) outcomes of Rh^{II}-catalyzed transformations of benzylidene **1** (ref. 17) and 2-pyridylmethylene **3** (ref. 20) substrates. *Reagents and conditions*: i, $Rh_2(OAc)_4$ (1 mol%), CH_2Cl_2, room temperature.

The results of the current study are outlined in Scheme 1. The initial Wittig reaction of *in situ* generated phosphonium ylide gave good to excellent yields of 2-hydroxybenzylidene succinimides **6a–i**. The latter were suitable substrates for the sulfonyl-azide-free diazo transfer[21] in aqueous acetonitrile. As the result, chemically stable diazo compounds **7a–i** were obtained in good to excellent yields (*cf.* refs. 17–19).Without further optimization, rhodium(II) carbene generation and intramolecular insertion reaction was triggered by $Rh_2(OAc)_4$ (1 mol%) (*i.e.*, under conditions identical to those applied in the preparation of indolizines **5**[17]). As the result, good to excellent yields of chromeno[2,3-*c*]pyrrole-1,3(2*H*,3a*H*)-diones **8a–i** were achieved (see Scheme 1).[†]

Having an exemplary set of thus synthesized new chromeno-[2,3-*c*]pyrrole-1,3(2*H*,3a*H*)-diones **8**, we set off to demonstrate that the same unsaturated tricyclic products can serve as the progenitors of dihydro-2*H*-chromenes with the same, unprecedented substitution pattern. To this end, we undertook hydrogenation of two exemplary compounds **8f,i** over Pd/C

[†] *General procedure for the preparation of compounds* **8a–i**. Salt $Rh_2(OAc)_4$ (1 mol%) was added to a stirred solution of corresponding diazo benzylidene succinimide **7** (2 mmol) in CH_2Cl_2. The reaction mixture was stirred to complete conversion of diazo compound (control by TLC) and subjected to column chromatography on silica gel (eluting with *n*-hexane–acetone, 2 : 1) to afford chromenes **8**.



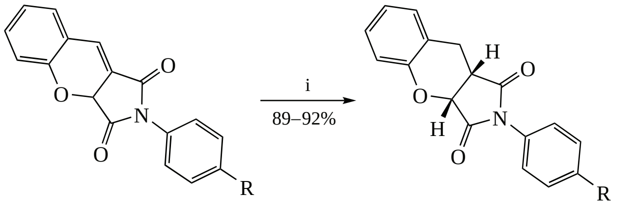
6a–i **7a–i** **8a–i**

a R^1 = Bn, $R^2 = R^3 = R^4 = R^5$ = H
b R^1 = 3-FC_6H_4, $R^2 = R^3 = R^4 = R^5$ = H
c R^1 = 4-FC_6H_4, $R^2 = R^3 = R^4 = R^5$ = H
d R^1 = 4-$MeOC_6H_4$, $R^2 = R^3 = R^4 = R^5$ = H
e R^1 = 4-$MeOC_6H_4$, $R^2 = R^3 = R^5$ = H, R^4 = Br
f R^1 = 4-MeC(O)C_6H_4, $R^2 = R^3 = R^4 = R^5$ = H
g R^1 = 4-$F_3CC_6H_4$, R^2 = MeO, $R^3 = R^4 = R^5$ = H
h R^1 = Ph, $R^2 = R^4$ = H, $R^3 = R^5$ = Me
i R^1 = 4-ClC_6H_4, $R^2 = R^3 = R^4 = R^5$ = H

Scheme 1 *Reagents and conditions*: i, PPh_3, MeOH, room temperature, 12 h; ii, K_2CO_3, 3-(chlorosulfonyl)benzoic acid, NaN_3, MeCN/water (7 : 1), room temperature, 20–24 h; iii, $Rh_2(OAc)_4$ (1 mol%), CH_2Cl_2, room temperature, 2–4 h.

catalyst.[‡] To our delight, both starting materials underwent a smooth, clean and high-yielding conversion to diastereomerically pure products **9a**,**b** in just 12 h, under ambient temperature and atmosphere (Scheme 2). The relative stereochemistry of compounds **9a**,**b** was assigned based on their NOESY spectra (see Online Supplementary Materials). It is of note that in the course of the catalytic hydrogenation of double bonds in substrates **8f**,**i**, acetyl and chlorine substituents remained intact.

In summary, we have described an unprecedented entry into 2*H*-chromene core *via* an intramolecular O–H insertion reaction of a Rh^{II} carbene generated from the earlier described type of diazo compounds, (*E*)-3-arylidene-4-diazopyrrolidine-2,5-diones, bearing a strategically positioned phenolic functionality. This approach resulted in the hitherto undescribed version of the privileged 2*H*-chromenes. Moreover, the latter can be easily and efficiently reduced to the corresponding dihydro-2*H*-chromenes akin to the naturally occurring scaffolds. These findings expand the scope of diazo chemistry application in the construction of medicinally relevant heterocycles. The compounds synthesized in this work will be made part of our biological screening program and any findings with regard to their biological activity will be followed up and reported on in due course.



7f,**i** **9a**,**b** **a** R = Ac
b R = Cl

Scheme 2 *Reagents and conditions*: i, Pd/C (10% w/w, 1 mol%), H_2 (1 atm.), THF (dry), 12 h.

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Online Supplementary Materials

Supplementary data associated with this article (experimental procedures, analytical data and copies of ^1H and ^{13}C NMR spectra) can be found in the online version at doi: 10.1016/j.mencom.2022.05.030.

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[‡] *General procedure for the preparation of compounds* **9f** *and* **9i**. To a solution of corresponding chromene **8** (1 mmol) in dry THF (10 ml), Pd/C (10% w/w, 1 mol%) was added and reaction mixture was stirred under H_2 atmosphere for 12 h. After completion of the reaction (TLC control), the catalyst was removed by centrifugation, the solvent was evaporated under reduced pressure and the crude product was purified by column chromatography on silica gel (eluting with *n*-hexane–acetone, 7 : 3).