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A multicomponent synthesis of gem-(β-dicarbonyl)arylmethanes

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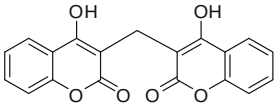
ABSTRACT

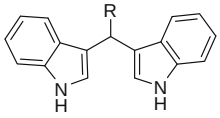
The reaction of aldehydes with β-dicarbonyls and electron-rich aromatics was investigated to generate in a multicomponent fashion crossed adducts of biological relevance. 4-Hydroxycoumarin, triacetic acid lactone, indole, and a selection of aliphatic and aromatic aldehydes representative of various electronic and steric conditions were employed. The reaction showed a surprising dependence on the solvent, with 1:1 chloroform–water giving the best yield of heterodimeric adducts. The mechanistic rationale for the formation of hetero- rather than homodimeric adducts is discussed.

The geminal bis(β-dicarbonyl)- and diheteroaryl-methane motif is featured in important bioactive natural products, like dicoumarol (**1**), the haemorrhagic principle of fermented sweet clover and the archetypal oral anticoagulant,[1] bis(3′-indolyl)methane (BIM, **2a**), a chemopreventive agent from cruciferous plants,[2] and 1,1-bis(3′-indolyl)ethane (BIE, **2b**), a bacterial self-growth inhibitor.[3] The synthesis of these homodimeric compounds is based on the condensation of aldehydes with electron-rich carbon nucleophiles (enols, etheroaromatics), a venerable reaction responsible for the observation that compounds **1**–**2b** were synthesized long before their actual biological relevance was recognized.[4] Heterodimeric (β-dicarbonyl)aryl methanes have instead received little attention, despite their potential relevance for the structure–activity relationships of their homodimeric analogues. As a consequence, their synthesis is still a substantially unchartered area.[5]

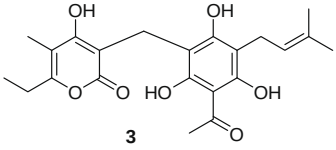
Our interest for this class of compounds was fostered by the remarkable bioactivity of the prenylated phloroglucinyl(pyronyl)methane arzanol (**3**) the major anti-inflammatory, antibiotic, and anti-oxidant principle of everlasting *Helichrysum italicum* [(Roth) G. Don].[6] Arzanol outperforms its corresponding homodimer helipyrone (**4**) in bioactivity assays, suggesting that the heterodimeric structure is critical for activity.[5] With the ultimate aim of developing a total synthesis of **3** and related heterodimeric pyrones, we have embarked in a systematic study on the synthesis of *gem*-(β-dicarbonyl)arylmethanes, exploring the possibility of obtaining this type of compound in a multicomponent fashion by combination of a carbonyl derivative with equimolar amounts of a β-dicarbonyl and an electron-rich aromatic.



1



2a R = H
2b R = CH_3



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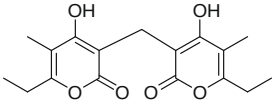

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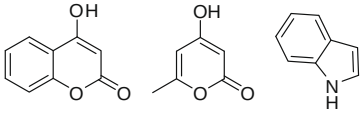

5 **6** **7**

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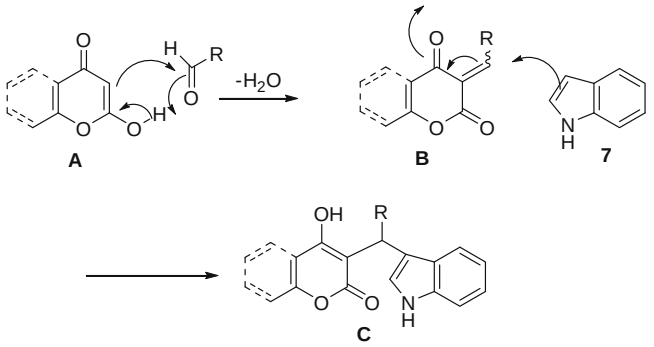
To combine proof of principle and biological relevance, we have taken inspiration from the structures of **1**–**3**, selecting 4-hydroxycoumarin (**5**) triacetic acid lactone (**6**), and indole (**7**) as the reacting partners. Aldehydes representative of various electronic and steric conditions were employed (acetaldehyde, heptanal, pivaladehyde, benzaldehyde and its *p*-methoxy- and *p*-nitro derivatives), while chloroform was used to optimize the reaction conditions because of the possibility to benefit from real-time NMR control when the deuterated version of the solvent was employed in exploratory experiments.

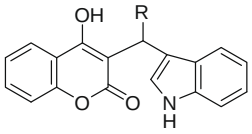
Mechanistic considerations point to the possibility of obtaining heterodimeric adducts from the reaction of aldehydes, β-dicarbonyls, and arenes. Thus, the hard aldehyde carbonyl is expected to react preferentially with the more localized nucleophilic double bond of an enol (Scheme 1, A) rather than with the softer and more dispersed π-system of an electron-rich aromatic. Conversely, the resulting Knoevenagel adduct (Scheme 1, B) is a softer electrophile, and should therefore react with an electron-rich aromatic nucleophile better than with an enolized β-dicarbonyl.[7]

Preliminary experiments (Table 1), while largely confirming these insights, also afforded several clues indicative of a more complex mechanistic scenario. Thus, when mixtures of adducts were obtained, only formation of bis-indolyl derivatives was observed, suggesting that indole can compete with the β-dicarbonyl nucleophile for attack to the aldehyde, or, alternatively, that indole can displace β-dicarbonyls from their heterodimeric adducts.[8] Furthermore, formation of homodimeric indolyl adducts was more marked with aromatic than with aliphatic aldehydes, and with triacetic acid lactone than with 4-hydroxycoumarin. To improve the yield of heterodimeric adducts, various solvent systems and catalysts were screened, eventually discovering that the use of a biphasic reaction system (chloroform–water 1:1) could steer the reaction toward the formation of heterodimeric adducts, solving, at least from a preparative standpoint, this issue (Table 1). Thus, while the reaction of *p*-nitrobenzaldehyde with 4-hydroxycoumarin and indole afforded an equimolecular mixture of the heterodimeric adduct **8d** and its corresponding bis-indolyl adduct, switching to $CHCl_3$–water provided the heterodimeric adduct **8d** in 85% yield. Occasionally, the heterodimeric adducts directly precipitated from the reaction mixture, while gravity column chromatography was required when a homogeneous reaction mixture was obtained.[9]

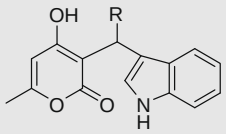


Scheme 1. Mechanism of the multicomponent reaction of aldehydes, β-dicarbonyls, and indole.

Table 1
Heterodimeric adducts from the multicomponent reaction of aldehydes, indole and 4-hydroxycoumarin (compounds **8a–e**) or triacetic acid lactone (compounds **9a–e**)



	R	Conditions (time, yield)*
8a	CH_3	a (5 h, 88%)
8b	C_6H_{13}	a (48 h, 70%)
8c	C_6H_5	a (24 h, 41%) b (48 h, 57%)
8d	$pNO_2C_6H_4$	a (24 h, 25%) b (48 h, 85%)
8e	$pOMeC_6H_4$	a (24 h, 18%) b (48 h, 28%)



9a	CH_3	a (6 h, 75%)
9b	C_6H_{13}	a (24 h, traces) b (24 h, 47%)
9c	C_6H_5	a (24 h, 21%) b (72 h, 26%)
9d	$pNO_2C_6H_4$	a (24 h, traces) b (72 h, 59%)
9e	$pOMeC_6H_4$	a (24 h, 18%) b (72 h, 12%)

* a: $CHCl_3$, 40 °C; b: $CHCl_3$–water 1:1, 40 °C.

Ultimately, heterodimeric adducts could be obtained from all aldehydes investigated except from pivaladehyde. This behavior is presumably due to steric hindrance from the bulky *t*-butyl group, that prevents the addition, in a Michael fashion, of a second nucleophilic species.[10]

The role of water to steer the reaction towards the formation of the heterodimeric adducts is difficult to rationalize, but goes beyond that of a mere precipitating agent for the generally poorly soluble heterodimeric adducts. Comparison of the results observed with heptanal and acetaldehyde upon reaction with indole (**7**) and triacetic acid lactone (**6**) exemplifies this issue. Thus, while acetaldehyde afforded a copious precipitate (75% yield) of the heterodimeric adduct **9a** when the reaction of heptanal was carried out under identical conditions, a homogeneous reaction mixture mainly containing heptyliden-bis-indolylmethane was obtained. However, when the reaction was performed in 1:1 chloroform–water, heptanal afforded a heterodimeric adduct (**9b**) as the major reaction product (47% isolated yield).

Taken together, our results, while pointing to new applications of multicomponent reactions and providing a straightforward entry into an interesting class of bioactive compounds, also raise a series of mechanistic issues worth further investigation.

Acknowledgments

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4. Dicoumarol was synthesized by Hanschutz as early as in 1909 (Hanschutz, R. *Liebigs Ann. Chem.* **1909**, *367*, 169–218).
5. Some β-dicarbonyl-heteroaryl cross dimers have been prepared in a two-step protocol from the condensation of heteroaryl aldehydes and β-dicarbonyls, followed by hydrogenation of the resulting Knoevenagel adducts with Pd/$CaCO_3$ (Velezheva, V. S.; Erofeev, Y. V.; Suvorov, N. N. *Zh. Org. Khim.* **1973**, 9, 185–9).
6. (a) Appendino, G.; Ottino, M.; Marquez, N.; Bianchi, F.; Ballero, M.; Sterner, O.; Fiebich, B. L.; Muñoz, E. *J. Nat. Prod.* **2007**, *70*, 608–612; (b) Rosa, A.; Deiana, M.; Atzeri, A.; Corona, G.; Melis, M. P.; Appendino, G.; Dessì, M. A. *Chem. Biol. Interact.* **2007**, *165*, 117–126.
7. Compared to enols, electron-rich aromatics are more polarizable, easier to oxidize, and therefore 'softer' (Ho, T. L. *Chem. Rev.* **1975**, *75*, 1–20).

8. An excess indole has been reported to displace 4-hydroxycoumarin from alkyliden-bis-4-hydroxycoumarins, affording mixtures of heterodimeric adducts and bisindolylmethanes (Appendino, G.; Cravotto, G.; Tagliapietra, S.; Ferraro, S.; Nano, G.M.; Palmisano, G. *Helv. Chim. Acta* **1991**, *74*, 1451–1458).
9. Typical reaction conditions: (a) With filtration work-up: To a stirred suspension of triacetic acid lactone (100 mg, 0.79 mmol) in $CHCl_3$ (2 mL), acetaldehyde (45 μL, 0.79 mmol) and indole (93 mg, 0.79 mmol) were sequentially added. The reaction was stirred at room temperature for 6 h, and then filtered. The precipitate was washed with $CHCl_3$ to afford 154 mg (75%) of **8a** as a white powder. Mp: 165 °C; IR (KBr) cm^{-1}: 3414, 2972, 2875, 2677, 1663, 1572, 1443, 1405, 1300, 1174, 1103, 934; ^1H NMR [300 MHz, $(CD_3)_2CO$]: δ 9.40 (s, 1H), 7.99 (s, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.30 (s, 1H), 7.02 (t, *J* = 8.0 Hz,, 1H), 6.91 (t, *J* = 8.0 Hz, 1H), 5.91 (s, 1H), 4.68 (q, *J* = 7.4 Hz, 1H), 2.08 (s, 3H), 1.67 (d, *J* = 7.4 Hz, 3H); ^{13}C NMR [75 MHz, $(CD_3)_2CO$]: 162.3 (s), 162.0 (s), 158.8 (s), 135.2 (s), 125.9 (s), 120.8 (d), 119.5 (d), 117.4 (d), 116.8 (d), 116.6 (s), 109.6 (d), 104.5 (s), 98.3 (d), 27.0 (d), 17.2 (q), 15.5 (q). (b) with chromatographic work-up: To a stirred suspension of triacetic acid lactone (107 mg, 0.85 mmol) in $CHCl_3/H_2O$ 1:1 (3 mL), heptanal (118 μL, 0.85 mmol) and indole (100 mg, 0.85 mmol) were sequentially added. The reaction was stirred at 40 °C overnight. The mixture was then directly chromatographed on silica gel (petroleum ether–EtOAc 7:3 as eluant) to afford 136 mg (47%) of **8a** as a powder. Mp: 72 °C; IR (KBr) cm^{-1}: 3414, 2953, 2869, 2667, 1673, 1567, 1445, 1403, 1288, 996, 832; ^1H NMR [300 MHz, $(CD_3)_2SO$]: 11.13 (s, 1H), 10.68 (s, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.30 (d, *J* = 1.8 Hz, 1H), 6.99 (t, *J* = 6.7 Hz, 1H), 6.88 (t, *J* = 6.7 Hz, 1H), 5.95 (s, 1H), 4.38 (dd, *J* = 9.5, 6.1 Hz, 1H), 2.24 (m, 1H), 2.08 (s, 3H), 1.95 (m, 1H), 1.18 (m, 8H), 0.84 (t, *J* = 6.1 Hz, 3H). ^{13}C NMR [75 MHz, $(CD_3)_2SO$]: 164.7 (s), 163.8 (s), 159.9 (s), 135.6 (s), 127.1 (s), 122.4 (d), 120.3 (d), 118.4 (d), 117.8 (d), 116.8 (s), 111.0 (d), 103.7 (s), 99.8 (d), 31.3 (t), 30.8 (q), 28.6 (t), 27.6 (t), 22.1 (t), 18.9 (q), 13.9 (q).
10. Appendino, G.; Cravotto, G.; Nano, G. M.; Palmisano, G.; Annunziata, R. *Helv. Chim. Acta* **1993**, *76*, 1194–1217.