

A facile and general synthesis of tropolonyl-substituted chalcone derivatives

Mingqin Chang^a, Yang Li^b, Hong Zhang^a and Wentao Gao^{b*}

^aCollege of Chemistry & Chemical Engineering, Bohai University, Jinzhou 121000, P. R. China

^bInstitute of Superfine Chemicals, Bohai University, Jinzhou 121 000, P. R. China

A facile and general synthesis of a series of new tropolonyl-substituted chalcone derivatives by Claisen–Schmidt condensation reaction from 3-acetyltropolone and substituted benzaldehydes as well as pyridine aldehydes is described. The method using 5% aq. KOH as catalyst and 50% aq. methanol as solvent is attractive since it specifically generates (*E*)-isomers with high yields under mild reaction conditions.

Keywords: tropolone, chalcone, Claisen–Schmidt condensation, aldehydes

In 1945, Dewar¹ predicted correctly the structure of tropolone (2-hydroxycyclohepta-2,4,6-trienone) based on the known natural products, colchicines and stipitatic acid.² In identifying the unique molecular structure (depicted in Fig. 1) of tropolone and its derivatives, *i.e.* a non-benzenoid “aromatic” compound, a new field in chemistry was launched. Since his discovery, tropolone natural products and synthetic tropolone derivatives have attracted considerable interest due to the unique structure and properties of the tropolone ring. Numerous tropolone natural products and several synthetic tropolone compounds have shown a range of potent biological activities.^{3–10} For example, some tropolones extracted from *Goupia glabra* exhibit significant toxicity towards a panel of DNA damage checkpoint defective yeast mutants, and behave as genotoxins, which highlights their potential to be used as anti-cancer drugs.¹¹ The tropolone moiety plays an important role in molecular assemblies for a fast and efficient lead generation in the new drug discovery. Despite featuring only seven-ring carbon atoms and no stereocentres, the synthesis of substituted tropolones continues to be a considerable synthetic challenge. Tropolone derivatives are scarce in nature,¹² occurring only in lower plants and fungi,¹³ and limited information is available on these compounds.

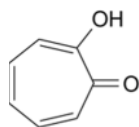


Fig. 1

On the other hand, the 1,3-diarylprop-2-enone (chalcone) moiety has earned the status of a privileged pharmacophore as compounds bearing this moiety possess a broad spectrum of biological activity.¹⁴ Recent studies on biological evaluation of chalcones revealed them to be anti-malarial,^{15–19} anti-cancer,^{20–22} anti-leishmanial,^{23–25} anti-inflammatory,^{26,27} antimitotic,²⁸ anti-tuberculosis,^{29,30} cardiovascular,³¹ cell differentiation inducing,³² nitric oxide regulation modulatory^{33,34} and anti-hyperglycemic agents.³⁵ Diarylprop-2-enones inhibit various enzymes such as CysLT₁,³⁶ COX/5-LOX,³⁷ EGFR tyrosine kinase³⁸ and tyrosinase³⁹ that play crucial roles in the biochemical pathways of different diseases. Recently, Nishida Jun *et al.* reported that some chalcone-bearing hydroxyl groups can act as potential inhibitors of tyrosinase.⁴⁰ Chalcones have also been considered the main biological precursors for the

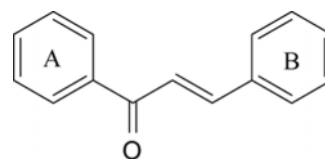


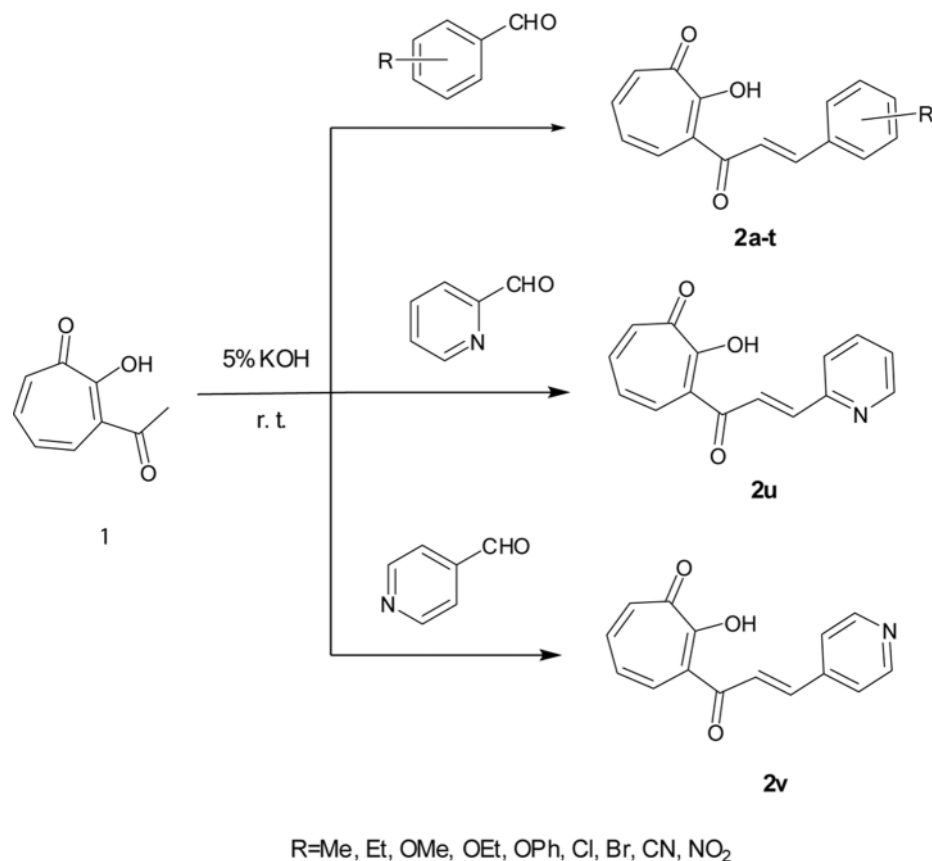
Fig. 2

biosynthesis of flavonoids, which are common components of the human diet.^{41–47} The complex pharmacological activities together with the easy synthetic reproduction and derivatisation of the core structure (depicted in Fig. 2) have caused considerable interest in the exploitation of the unique chalcone template for the discovery of prospective lead compounds.

In light of these findings and in view of the rapid assembly of molecular diversity being an important goal of synthetic organic chemistry as well as one of the key paradigms of modern drug discovery, a general and broad synthesis of tropolonyl-substituted chalcone compounds would be very attractive. Moreover, this kind of tropolonyl-substituted chalcone derivatives can be useful precursors for the synthesis of several unusually heterocycle-fused tropolone compounds as well as more complex systems. But as far as we know, only few reports exist for the synthesis of tropolonyl-substituted chalcones.^{48–50} However, all these reports are of individual syntheses and are just limited to the synthesis of several methoxy- or heterocycle-substituted derivatives. No efforts have been made to develop a general synthetic approach. Therefore it is of interest to find a general synthesis of a wide variety of tropolonyl-substituted chalcone derivatives and the results of our investigations in this field are reported herein.

As shown in Scheme 1, 22 new tropolone-substituted chalcones **2a–v** were readily prepared by using Claisen–Schmidt condensation of 3-acetyltropolone (**1**) with various substituted aldehydes (1.5 molar equiv.) with 5% aqueous KOH as catalyst at room temperature for 24 h. These conditions were found to be satisfactory for the synthesis of the derivatives in good to excellent yields. The experimental procedure was very simple. In all cases, the products were isolated by simple filtration in practically pure form. The current method was fairly general, clean, and efficient, providing an expeditious access to the preparation of various tropolone-substituted chalcones. It is noteworthy that if the reagents are added simultaneously to 50% aqueous methanol, or 5% KOH solution is added first, none of the desired products were obtained. Only when 5% KOH solution was added dropwise slowly to the 50% methanol solution of aldehyde and 3-acetyltropolone under stirring did the reaction proceed as shown. The results summarised

* Correspondent. E-mail: bhuzh@163.com

**Table 1** Melting points, yields and MS data of compounds **2a–v**

Entry	Compd	R	M.p./°C	Yield/%	MS (ES+) m/z [M+H] ⁺
1	2a	3-Me	129–130	84	267.2
2	2b	4-Me	180–181	93	267.2
3	2c	4-Et	165–167	79	281.1
4	2d	2-OEt	136–138	83	297.1
5	2e	4-OEt	170–172	87	297.1
6	2f	3-OPh	120–122	84	345.1
7	2g	2-Cl	160–161	91	287.1
8	2h	3-Cl	182–184	82	287.1
9	2i	4-Cl	184–186	92	287.1
10	2j	2-Br	162–164	85	330.7 (⁷⁹ Br)
11	2k	3-Br	176–178	84	331.4 (⁷⁹ Br)
12	2l	4-Br	200–201	89	331.1 (⁷⁹ Br)
13	2m	3-NO ₂	236–238	83	298.1
14	2n	4-NO ₂	205–207	84	298.1
15	2o	4-CN	220–222	89	278.2
16	2p	2,3-(Cl) ₂	218–220	92	321.1 (³⁵ Cl)
17	2q	2,4-(Cl) ₂	220–222	80	321.1 (³⁵ Cl)
18	2r	2,6-(Cl) ₂	166–167	89	320.7 (³⁵ Cl)
19	2s	3,4-(Cl) ₂	242–244	78	321.1 (³⁵ Cl)
20	2t	3,5-(Cl) ₂	254–256	83	321.0 (³⁵ Cl)
21	2u	–	194–196	50	254.1
22	2v	–	210–212	48	254.1

in Table 1 indicate the scope and generality of the Claisen–Schmidt reaction of 3-acetyltropolone with the various substituted aldehydes.

The Claisen–Schmidt condensation reaction of 3-acetyltropolone with different aldehydes proved to be efficient furnishing excellent yields of the corresponding tropolone-substituted chalcones. For example, the tropolone-substituted chalcones **2a–f** (entries 1–6) bearing electron-donating substituents such

as methyl, ethyl, ethoxy and phenoxy groups on the benzene ring, were obtained in 79–93% yields. Similarly, the other products **2g–t** (entries 7–20) bearing electron-withdrawing groups such as halo-, nitro-, cyano- in *ortho*-, *meta*- and *para*-positions were obtained in 78–92% yields. Thus we concluded that the effect of substituent groups is not very strong. However, in the Claisen–Schmidt condensation reaction using 2-pyridine aldehyde or 3-pyridine aldehyde, the corresponding

Table 2 Spectroscopic data of compounds **2a–v**

Compd.	IR, ν /cm ⁻¹	¹ H NMR, δ (J in Hz)	HR-ESI-MS (m/z) Found (Calcd)
2a	3193 (OH), 1651 (C=O), 1612 (C=O), 1557 (Ar)	2.36 (s, 3H, CH ₃), 7.12–7.14 (m, 1H, ArH), 7.18 (d, 1H, J = 16.0 Hz, H- α), 7.22–7.29 (m, 2H, ArH), 7.37–7.42 (m, 3H, ArH), 7.48 (d, 1H, J = 10 Hz, ArH), 7.61 (d, 1H, J = 16.0 Hz, H- β), 7.68 (d, 1H, J = 10 Hz, ArH)	289.0836 [M+Na] ⁺ C ₁₇ H ₁₄ NaO ₃ ⁺ (289.0835)
2b	3197 (OH), 1650 (C=O), 1617 (C=O), 1560 (Ar)	2.38 (s, 3H, CH ₃), 7.12–7.26 (m, 5H, ArH and H- α), 7.40–7.52 (m, 3H, ArH), 7.61 (d, 1H, J = 16.0 Hz, H- β), 7.67 (d, 1H, J = 10.0 Hz, ArH)	289.0830 [M+Na] ⁺ C ₁₇ H ₁₄ NaO ₃ ⁺ (289.0835)
2c	3190 (OH), 1665 (C=O), 1607 (C=O), 1542 (Ar)	1.24 (t, 3H, J = 7.6 Hz, CH ₂ CH ₃), 2.67 (q, 2H, J = 7.6 Hz, CH ₂ CH ₃), 7.12–7.26 (m, 4H, ArH and H- α), 7.40–7.51 (m, 4H, ArH), 7.62 (d, 1H, J = 15.6 Hz, H- β), 7.68 (d, 1H, J = 9.6 Hz, ArH)	303.0993 [M+Na] ⁺ C ₁₈ H ₁₆ NaO ₃ ⁺ (303.0992)
2d	3193 (OH), 1649 (C=O), 1615 (C=O), 1572 (Ar)	1.42 (t, 3H, J = 7.0 Hz, OCH ₂ CH ₃), 4.08 (q, 2H, J = 7.0 Hz, OCH ₂ CH ₃), 6.95–6.87 (m, 2H, ArH), 7.12 (d, 1H, J = 10.0 Hz, ArH), 7.26–7.37 (m, 3H, ArH), 7.42 (d, 1H, J = 15.2 Hz, H- α), 7.56 (d, 1H, J = 7.6 Hz, ArH), 7.66 (d, 1H, J = 9.6 Hz, ArH), 7.96 (d, 1H, J = 15.6 Hz, H- β)	319.0945 [M+Na] ⁺ C ₁₈ H ₁₆ NaO ₄ ⁺ (319.0941)
2e	3171 (OH), 1660 (C=O), 1600 (C=O), 1552 (Ar)	1.42 (t, 3H, J = 7.0 Hz, OCH ₂ CH ₃), 4.06 (q, 2H, J = 7.0 Hz, OCH ₂ CH ₃), 6.88 (d, 2H, J = 8.4 Hz, ArH), 7.10 (d, 1H, J = 15.6 Hz, H- α), 7.38–7.52 (m, 4H, ArH), 7.58 (d, 1H, J = 15.6 Hz, H- β), 7.65 (d, 2H, J = 10.0 Hz, ArH)	319.0948 [M+Na] ⁺ C ₁₈ H ₁₆ NaO ₄ ⁺ (319.0941)
2f	3198 (OH), 1659 (C=O), 1601 (C=O), 1565 (Ar)	7.00–7.04 (m, 3H, ArH), 7.13–7.15 (m, 3H, ArH), 7.18 (d, 1H, J = 16.0 Hz, H- α), 7.33–7.42 (m, 5H, ArH), 7.48 (d, 1H, J = 10.0 Hz, ArH), 7.57 (d, 1H, J = 16.0 Hz, H- β), 7.68 (d, 1H, J = 10.0 Hz, ArH)	367.0947 [M+Na] ⁺ C ₂₂ H ₁₆ NaO ₄ ⁺ (367.0941)
2g	3202 (OH), 1660 (C=O), 1610 (C=O), 1551 (Ar)	7.14–7.17 (m, 1H, ArH), 7.21 (d, 1H, J = 15.7 Hz, H- α), 7.26–7.34 (m, 2H, ArH), 7.42 (d, 2H, J = 10.2 Hz, ArH), 7.49–7.55 (m, 1H, ArH), 7.72–7.77 (m, 2H, ArH), 8.08 (d, 1H, J = 15.7 Hz, H- β)	309.0284 [M+Na] ⁺ C ₁₆ H ₁₁ ³⁵ ClNaO ₃ ⁺ (309.0289)
2h	3201 (OH), 1672 (C=O), 1611 (C=O), 1550 (Ar)	7.13–7.17 (m, 1H, ArH), 7.29 (d, 1H, J = 16.4 Hz, H- α), 7.34 (s, 1H, ArH), 7.42–7.58 (m, 5H, ArH and H- β), 7.70 (d, 1H, J = 7.2 Hz, ArH), 7.85 (s, 1H, ArH)	309.0285 [M+Na] ⁺ C ₁₆ H ₁₁ ³⁵ ClNaO ₃ ⁺ (309.0289)
2i	3198 (OH), 1658 (C=O), 1612 (C=O), 1563 (Ar)	7.17–7.19 (m, 1H, ArH), 7.21 (d, 1H, J = 15.6 Hz, H- α), 7.26–7.32 (m, 2H, ArH), 7.42 (d, 2H, J = 10.4 Hz, ArH), 7.51 (d, 1H, J = 10.0 Hz, ArH), 7.72–7.77 (m, 2H, ArH), 8.08 (d, 1H, J = 15.0 Hz, H- β)	309.0288 [M+Na] ⁺ C ₁₆ H ₁₁ ³⁵ ClNaO ₃ ⁺ (309.0289)
2j	3210 (OH), 1660 (C=O), 1609 (C=O), 1541 (Ar)	7.13–7.18 (m, 1H, ArH), 7.22 (d, 1H, J = 16.0 Hz, H- α), 7.32 (d, 1H, J = 10.4 Hz, ArH), 7.35–7.44 (m, 2H, ArH), 7.51–7.56 (m, 1H, ArH), 7.60–7.68 (m, 2H, ArH), 7.77 (d, 1H, J = 16.0 Hz, H- β), 7.87–7.91 (m, 1H, ArH).	352.9780 [M+Na] ⁺ C ₁₆ H ₁₁ ⁷⁹ BrNaO ₃ ⁺ (352.9784)
2k	3205 (OH), 1671 (C=O), 1608 (C=O), 1549 (Ar)	7.14–7.16 (m, 2H, ArH), 7.21 (d, 1H, J = 16.0 Hz, H- α), 7.25–7.30 (m, 1H, ArH), 7.42 (d, 1H, J = 10.0 Hz, ArH), 7.50–7.55 (m, 3H, ArH), 7.58 (d, 1H, J = 16.0 Hz, H- β), 7.74 (d, 1H, J = 10.4 Hz, ArH).	352.9785 [M+Na] ⁺ C ₁₆ H ₁₁ ⁷⁹ BrNaO ₃ ⁺ (352.9784)
2l	3194 (OH), 1650 (C=O), 1611 (C=O), 1562 (Ar)	7.07–7.12 (m, 1H, ArH), 7.21 (d, 1H, J = 16.0 Hz, H- α), 7.26–7.29 (m, 3H, ArH), 7.45–7.52 (m, 3H, ArH), 7.57 (d, 1H, J = 16.0 Hz, H- β), 7.61–7.64 (m, 1H, ArH)	352.9783 [M+Na] ⁺ C ₁₆ H ₁₁ ⁷⁹ BrNaO ₃ ⁺ (352.9784)
2m	3210 (OH), 1680 (C=O), 1612 (C=O), 1529 (Ar)	7.00–7.17 (m, 2H, ArH), 7.41–7.47 (m, 2H, ArH and H- α), 7.63 (d, 1H, J = 10.8 Hz, ArH), 7.81 (d, 1H, J = 8.0 Hz, ArH), 7.86–7.90 (m, 2H, ArH), 8.43 (d, 1H, J = 15.6 Hz, H- β), 8.45 (d, 1H, J = 5.6 Hz, ArH)	296.0565 [M-H] ⁻ C ₁₆ H ₁₀ NO ₃ ⁻ (296.0564)
2n	3200 (OH), 1677 (C=O), 1610 (C=O), 1550 (Ar)	7.02–7.07 (m, 2H, ArH), 7.13 (d, 1H, J = 15.6 Hz, H- α), 7.35–7.42 (m, 3H, ArH), 7.48 (d, 1H, J = 4.4 Hz, ArH), 7.60 (d, 1H, J = 16.0 Hz, H- β), 8.50 (d, 1H, J = 5.2 Hz, ArH), 8.62 (d, 1H, J = 5.2 Hz, ArH)	320.0522 [M+Na] ⁺ C ₁₆ H ₁₁ NNaO ₅ ⁺ (320.0529)
2o	3210 (OH), 1674 (C=O), 1617 (C=O), 1550 (Ar)	7.16–7.21 (m, 1H, ArH), 7.38 (d, 1H, J = 16.0 Hz, H- α), 7.44 (d, 1H, J = 10.0 Hz, ArH), 7.52–7.57 (m, 5H, ArH), 7.67 (d, 1H, J = 15.6 Hz, H- β), 7.82 (d, 1H, J = 9.6 Hz, ArH)	300.0632 [M+Na] ⁺ C ₁₇ H ₁₁ NNaO ₃ ⁺ (300.0631)
2p	3200 (OH), 1675 (C=O), 1610 (C=O), 1564 (Ar)	7.15–7.21 (m, 2H, ArH), 7.23–7.26 (m, 2H, ArH), 7.35–7.39 (m, 2H, ArH), 7.43 (d, 1H, J = 16.4 Hz, H- α), 7.49–7.54 (m, 1H, ArH), 7.80 (d, 1H, J = 16.4 Hz, H- β)	342.9891 [M+Na] ⁺ C ₁₆ H ₁₀ ³⁵ Cl ₂ NaO ₃ ⁺ (342.9899)
2q	3200 (OH), 1670 (C=O), 1613 (C=O), 1557 (Ar)	7.14–7.19 (m, 1H, ArH), 7.34 (d, 1H, J = 15.8 Hz, H- α), 7.36 (s, 1H, ArH), 7.50 (d, 1H, J = 12.0 Hz, ArH), 7.57 (d, 1H, J = 12.0 Hz, ArH), 7.63–7.66 (m, 2H, ArH), 7.74 (d, 1H, J = 15.8 Hz, H- β), 7.97 (d, 1H, J = 8.0 Hz, ArH)	342.9898 [M+Na] ⁺ C ₁₆ H ₁₀ ³⁵ Cl ₂ NaO ₃ ⁺ (342.9899)
2r	3201 (OH), 1665 (C=O), 1612 (C=O), 1550 (Ar)	7.15–7.20 (m, 1H, ArH), 7.32–7.36 (m, 2H, ArH), 7.43 (d, 1H, J = 15.9 Hz, H- α), 7.54 (d, 1H, J = 10.2 Hz, ArH), 7.66 (d, 1H, J = 9.4 Hz, ArH), 7.72 (d, 1H, J = 7.8 Hz, ArH), 7.82 (d, 1H, J = 15.9 Hz, H- β), 7.91 (d, 1H, J = 7.8 Hz, ArH)	342.9890 [M+Na] ⁺ C ₁₆ H ₁₀ ³⁵ Cl ₂ NaO ₃ ⁺ (342.9899)
2s	3218 (OH), 1670 (C=O), 1609 (C=O), 1548 (Ar)	7.13–7.18 (m, 1H, ArH), 7.32 (d, 1H, J = 16.0 Hz, H- α), 7.49–7.58 (m, 4H, ArH and H- β), 7.68 (d, 1H, J = 8.0 Hz, ArH), 7.75 (d, 1H, J = 8.4 Hz, ArH), 8.08 (s, 1H, ArH)	342.9891 [M+Na] ⁺ C ₁₆ H ₁₀ ³⁵ Cl ₂ NaO ₃ ⁺ (342.9899)
2t	210 (OH), 1675 (C=O), 1611 (C=O), 1557 (Ar)	7.13–7.17 (m, 1H, ArH), 7.32 (d, 1H, J = 10.3 Hz, ArH), 7.38 (d, 1H, J = 16.1 Hz, H- α), 7.48–7.58 (m, 3H, ArH and H- β), 7.66 (s, 1H, ArH), 7.87 (s, 2H, ArH)	318.9931 [M-H] ⁻ C ₁₆ H ₉ Cl ₂ O ₃ ⁻ (318.9934)
2u	3105 (OH), 1660 (C=O), 1594 (C=O), 1551 (Ar)	6.99–7.06 (m, 2H, ArH), 7.20 (d, 1H, J = 15.8 Hz, H- α), 7.38–7.44 (m, 2H, ArH), 7.51–7.55 (m, 2H, ArH), 7.73 (d, 1H, J = 15.8 Hz, H- β), 8.52–8.57 (m, 1H, ArH), 8.62–8.65 (m, 1H, ArH)	254.0814 [M+H] ⁺ C ₁₅ H ₁₂ O ₃ ⁺ (254.0812)
2v	3200 (OH), 1670 (C=O), 1609 (C=O), 1542 (Ar)	7.07–7.16 (m, 2H, ArH), 7.28 (d, 1H, J = 15.8 Hz, H- α), 7.44–7.51 (m, 1H, ArH), 7.56–7.62 (m, 1H, ArH), 7.77 (d, 1H, J = 8.0 Hz, ArH), 7.83–7.91 (m, 2H, ArH), 7.99 (d, 1H, J = 15.8 Hz, H- β), 8.17–8.20 (m, 1H, ArH)	254.0816 [M+H] ⁺ C ₁₅ H ₁₂ O ₃ ⁺ (254.0812)

products **2u** and **2v** (entries 21 and 22) were obtained in only moderate yields of 50% and 48%, respectively. We also attempted to increase to three- to five-fold the excess of KOH (15–25%) but this was found to decrease the yields of the two products due to the occurrence of some side reactions like 1,4-Michael additions. All the synthesised compounds have not been reported previously and their structures were confirmed by spectroscopic data, which are listed in Table 2.

All spectroscopic data are in accordance with the described structures. The molecular formulae were usually established from the *quasi*-molecular ion $[M+Na]^+$ peak of, indicating the presence of the positive-mode HR-ESI-MS 11 degrees of unsaturation. Different procedures were used for **2m**, **2t**, **2u** and **2v**. In the IR spectra of compounds **2a–v**, the absorptions relating to an α,β -unsaturated carbonyl moiety stretch were observed at 1594–1615 cm^{-1} and tropolone carbonyl moiety stretching frequency in 1649–1680 cm^{-1} . The ^1H NMR spectra for all the synthesised compounds show the signals of aromatic hydrogens between 6.88 and 8.62 ppm. The main features of the ^1H NMR data are the resonances of the vinylic protons appearing as doublets at δ_{Ha} 7.10–7.43 ppm and δ_{HB} 7.57–7.99 ppm. The coupling constants $^3J_{\text{Ha-HB}}$, in the range of 15.6–16.4 Hz indicate the *E*-configuration of these vinylic systems. As reported in the chalcone literature⁵¹, the Claisen–Schmidt condensation reaction yields only *E*-stereoisomers.

In conclusion, the present investigation has demonstrated a general synthesis of a wide variety of tropolonyl-substituted chalcone derivatives in good to excellent yields. The numerous molecules we have synthesised should allow us to investigate structure–activity relationships over various biotests. In addition, as chalcone derivatives these molecules can provide a bifunctional site for 1,3-dinucleophiles affording heterocyclic ring-systems, and thus will be used as useful synthons in tropenoid chemistry.

Experimental

Melting points (uncorrected) were determined using a WRS-1B melting points apparatus. ^1H NMR spectra were measured with a Bruker BRX 400 instrument at 400 MHz. The reported chemical shifts are relative to TMS. Mass spectra were recorded on a Micromass Platform liquid chromatography mass spectrometry-electrospray ionisation. HRMS (ESI) data were acquired on an Bruker Customer micrOTOF-Q 125 high-resolution mass spectrometer.

Tropolone-substituted chalcone derivatives 3-(3-arylacryloyl) tropolones (2a–t) or 3-(3-pyridinylacryloyl)tropolones (2u–v), general procedure

To a stirred solution of 3-acetyltropolone (1 mmol, 0.164 g) and the appropriate benzaldehyde or pyridine aldehyde (1.5 mmol), an aqueous solution of 5% KOH (5 mL) was added dropwise. The resulting solution was stirred at room temperature for 24 h. The reaction mixture was quenched by addition of 5 mL H_2O and acidification with 1 M HCl. The precipitate was collected by filtration, washed with water, dried, and recrystallised from methanol to give products **2a–v** in 48–97% yields.

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