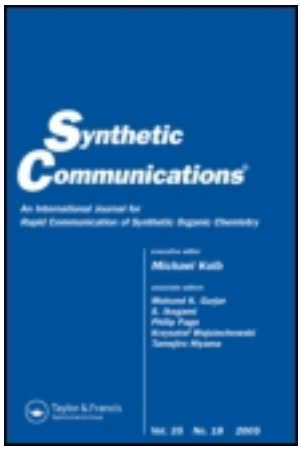

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A FACILE SYNTHESIS OF 3,4-DIHYDRO- 2-PYRONYL-1,5-BENZODIAZEPINE DERIVATIVES

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A FACILE SYNTHESIS OF 3,4-DIHYDRO-2-PYRONYL-1,5-BENZODIAZEPINE DERIVATIVES

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ABSTRACT

The reaction of *o*-phenylenediamine with 3-cinnamoyl-4-hydroxy-6-methyl-2-pyrones (**3a–i**, chalcone analogs of dehydroactic acid) in ethanol-acetic acid provides a facile method for the synthesis of 3,4-dihydro-2-pyronyl-1,5-benzodiazepine derivatives (**2a–i**).

The importance of 1,5-benzodiazepines and their derivatives as therapeutic agents with widespread biological activity is well established.[1] Fodili et al.[2] have recently reported the synthesis of a few 3,4-dihydro-2-pyronyl-1,5-benzodiazepines (**2**) by the reaction of dehydroacetic acid (DHA) and *o*-phenylenediamine (OPD), followed by treatment of the resulting ketimine **1** with aromatic aldehydes in the presence of a catalytic amount

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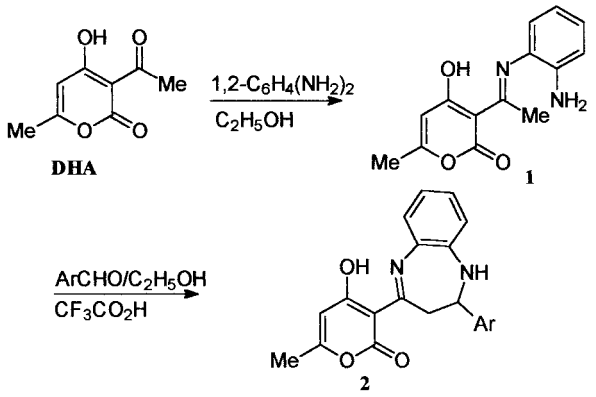
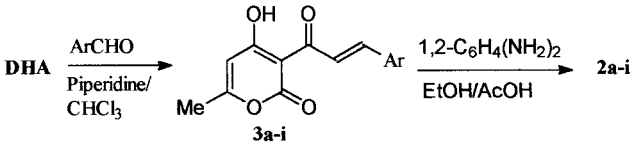
of trifluoroacetic acid (Scheme A). As part of our ongoing studies on the reactions and synthetic applications of DHA and its derivatives,[3] we report herein an alternate and facile method for the synthesis of **2** by the reaction of OPD with 3-cinnamoyl-4-hydroxy-6-methyl-2-pyrones (**3**, chalcone analogs of DHA).

The chalcones analogs of DHA (**3a–i**), prepared according to the literature procedure[4] by the condensation of DHA with various aldehydes, were treated with one equivalent of OPD in ethanol-acetic acid. The reaction afforded the desired 1,5-benzodiazepine derivatives **2a–i** in high yields (Scheme 1). The results of this reaction along with the data of the products are summarized in Table 1.



Scheme A.



2,3	Ar	2,3	Ar	2,3	Ar
a	C_6H_5	d	4-OHC_6H_4	g	4-$(CH_3)_2NC_6H_4$
b	4-ClC_6H_4	e	2-OHC_6H_4	h	4-$O_2NC_6H_4$
c	4-$CH_3C_6H_4$	f	4-$CH_3OC_6H_4$	i	2-Thienyl

Scheme 1.

Table 1. Benzodiazepines **2a–i**, Prepared According to Scheme 1

Benzodiazepines	M.P. (°C) (Literature M.P.)[2]	Yield (%)[a]	Molecular Formula
2a	218–220 (226)	78	[b]
2b	228–230 (240)	79	[b]
2c	229–230 (230)	86	[b]
2d	238–240 (238)	86	[b]
2e	239–240 (238–240)	82	[b]
2f	226–228 (240)	85	[b]
2g	224–225	86	$C_{23}H_{23}N_3O_3$[c]
2h	152–154	76	$C_{21}H_{17}N_3O_5$[c]
2i	183–184	80	$C_{19}H_{16}N_2O_3S$[c]

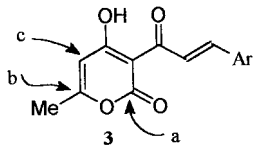
[a]Yields of isolated products w.r.t. the quantity of chalcone analog **3**.
[b]Spectral properties (IR, ^{1}H NMR and MS) were in full agreement with those reported previously. The spectral data for the new products (**2g–i**) are given: **2g**, IR (nujol) (ν cm^{-1}) 3326, 1704, 1655. ^{1}H NMR ($CDCl_3$): δ 2.87 (dd, 1H, $J = 11.2$ Hz, 10.8 Hz, CH_2), 4.36 (dd, 1H, $J = 11.2$ Hz, 2.9 Hz, CH_2), 5.19 (dd, 1H, $J = 10.8$ Hz, 2.9 Hz, *p*-$NMe_2C_6H_4CH$), 3.99 (s, 1H, NH), 2.15 (s, 3H, CH_3), 5.76 (s, 1H, CH=C), 6.69–7.72 (m, 8H, arom), 15.49 (s, 1H, OH), 2.94 (s, 6H, NMe_2); **2h**, IR (nujol) (ν cm^{-1}) 3399, 1705, 1644. ^{1}H NMR ($CDCl_3$): δ 3.39 (dd, 1H, $J = 12.8$ Hz, 9.7 Hz, CH_2), 4.05 (dd, 1H, $J = 12.8$ Hz, 3.2 Hz, CH_2), 5.44 (dd, 1H, $J = 9.7$ Hz, 3.2 Hz, *p*-$NO_2C_6H_4CH$), 3.88 (s, 1H, NH), 2.14 (s, 3H, CH_3), 5.75 (s, 1H, CH=C), 6.69–8.19 (m, 8H, arom), 15.48 (s, 1H, OH); **2i**, IR (nujol) (ν cm^{-1}) 3309, 1694, 1656. ^{1}H NMR ($CDCl_3$): δ 2.98 (dd, 1H, $J = 12.2$ Hz, 10.7 Hz, CH_2), 4.37 (dd, 1H, $J = 12.2$ Hz, 3.7 Hz, CH_2), 5.61 (dd, 1H, $J = 10.7$ Hz, 3.7 Hz, 2-thineyl CH), 3.99 (s, 1H, NH), 2.16 (s, 3H, CH_3), 5.77 (s, 1H, CH=C), 6.88–7.2 (m, 7H, arom), 15.45 (s, 1H, OH).
[c]Elemental analyses (C, H, N, S) were satisfactory.

The noteworthy features, which account for the significance of the new route for the synthesis of **2a–i**, are:

(a) The method involving simple experimentation is quite general as various substituted DHA chalcone analogs (**2a–i**) are smoothly converted to the corresponding 1,5-benzodiazepines **2a–i**.
(b) The *p*-nitrophenyl derivative **2h**, which could not be synthesized by the method used by Fodili et al.,[2] is easily accessible through the present approach.
(c) Three new 1,5-benzodiazepines **2g**, **2h** and **2i** (2-thienyl analog) are also available.
(d) The quantity of aldehydes employed in the present procedure is one equivalent with respect to the quantity of DHA and OPD as

compared to 1.5–3.0 equivalents of the aldehydes used in the reported procedure.[2]

(e) The other electrophilic sites (indicated as *a–c*) present in the structure of **3** remain unaffected.[5]



EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. ^{1}H NMR spectra were recorded on Brucker 300 MHz instrument using TMS as an internal standard. Chalcone analogous **3a–i** were prepared according to literature procedure.[4]

Conversion of Substituted 3-Cinnamoyl-4-hydroxy-6-methyl-2-pyrones (3a–i) to 3,4-Dihydro-2-pyronyl-1,5-benzodiazepine Derivatives (2a–i)

General procedure: To a solution of **3** (1 mmol) in ethanol (20 mL) was added a few drops of piperidine and *o*-phenylenediammine (1 mmol, 108 mg). The mixture was heated under reflux for 3–4 h and then added 1 mL of AcOH. The refluxing was continued for another 3–4 h. About half of the solvent was distilled off and the resulting mixtures was allowed to stand at room temperature overnight. The crystalline solid product **2** thus separated was filtered, washed with 2–3 mL of cold aq. ethanol (50 : 50 by v/v) and dried (Table 1).

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REFERENCES

1. Katritzky, A.R.; Abonia, R.; Yang, B.; Qi, M.; Insuasty, B. Synthesis **1998**, 1487 and references therein.

2. Fodili, M.; Amari, M.; Kolli, B.; Robert, A.; Floc'h, M.B.; Grel, P.L. Synthesis **1999**, 811.
3. (a) Singh, S.P.; Prakash, O.; Vaid, R.K. Indian J. Chem. **1984**, *23B*, 191; (b) Singh, S.P.; Tarar, L.S.; Kumar, D. Synth. Commun. **1993**, *23*, 1855; (c) Singh, S.P.; Tarar, L.S.; Kumar, D. Indian J. Heterocycl. Chem. **1993**, *3*, 5.
4. Wiley, R.H.; Jarboe, C.H.; Elert, H.G. J. Am. Chem. Soc. **1955**, *77*, 5102.
5. Chrgui, D.; Hamdi, M.; Baboulene, M.; Speziale, V.; Lattes, A. J. Heterocycl. Chem. **1986**, *23*, 1721.

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