A Simple, One-Step Synthesis of 3,4-Dihydro-4-phenacyl-2*H*-1,3-benzoxazin-2-ones

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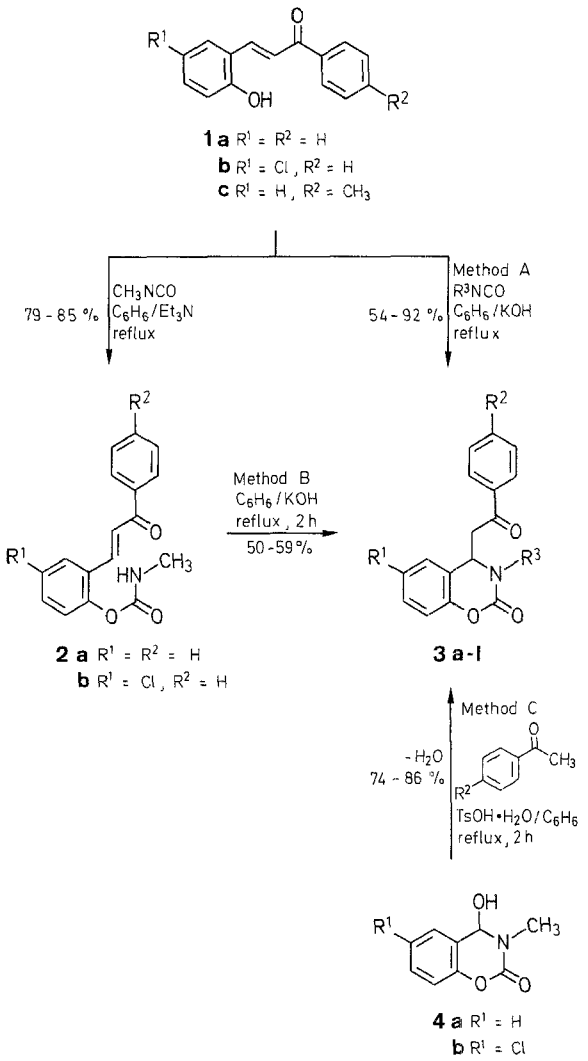
2-Hydroxychalcones **1a, b** react readily with alkyl and aryl isocyanates in the presence of potassium hydroxide to give directly the corresponding 3-alkyl- and 3-aryl-3,4-dihydro-4-phenacyl-2*H*-1,3-benzoxazin-2-ones **3**. The 2-thione analogues **5a, b** are similarly obtained by reacting **1a, b** with methyl isothiocyanate. Thiones **5** are readily oxidized by yellow mercuric oxide to the corresponding oxo compounds **3**. The direct formation of benzoxazinones from chalcones apparently proceeds through the intermediate formation of open chain carbamates. The latter are cleaved readily by *p*-toluenesulfonyl chloride under base catalysis to give the corresponding sulfonates.

Although a wide variety of *N*-substituted 3,4-dihydro-2*H*-1,3-benzoxazin-2-ones have been prepared by condensing 3,4-dihydro-4-hydroxy-2*H*-1,3-benzoxazin-2-ones **4** (*N*-alkyl or *N*-cycloalkyl) with the appropriate active hydrogen compound,[1-3] nothing has been reported on the synthesis of the *N*-aryl analogues by this method, presumably due to the difficult accessibility of the *N*-aryl derivatives of **4**. Meanwhile, only one example, **3c**, of a 4-phenacyl derivative has been described,[1] which was prepared also by this method.

The present communication outlines a new, facile, versatile one-step synthesis of the title compounds, including the hitherto unknown *N*-aryl analogues. It is found that methyl isocyanate reacts with chalcones **1a, b** in dry refluxing benzene containing catalytic amounts of solid potassium hydroxide to directly give the 3,4-dihydro-3-methyl-4-phenacyl-2*H*-1,3-benzoxazin-2-ones **3a, b** in good yield (Method A). The structure of the products is inferred from elemental analysis, lack of color, spectral features and chemical properties. Their IR spectra lack ν_{NH}, thus excluding open chain carbamate structures **2a, b** which possibly could be formed. Thus, the IR spectra of compounds 3 show bands due to ketonic and carbamoyloxy carbonyls (cf.



3	R^1	R^2	R^3	3	R^1	R^2	R^3
a	H	H	CH_3	**g**	H	H	C_6H_5
b	Cl	H	CH_3	**h**	Cl	H	C_6H_5
c	H	CH_3	CH_3	**i**	H	H	*p*-ClC_6H_4
d	Cl	CH_3	CH_3	**j**	Cl	H	*p*-ClC_6H_4
e	H	H	C_2H_5	**k**	H	H	1-naphthyl
f	Cl	H	C_2H_5	**l**	Cl	H	1-naphthyl

Table). Their UV spectra are devoid of the long wave absorption due to the α,β-unsaturated ketonic moiety of the parent chalcones; however, they exhibit the strong K absorption due to the aroyl moiety. Their ^{1}H-NMR spectra exhibit signals for an ABX system due to coupled protons of the CH–CH_2 moiety. The products give 2,4-dinitrophenylhydrazones and their molecular weights, determined by MS, are in agreement with the assigned structure.

3,4-Dihydro-2*H*-1,3-benzoxazin-2-ones **3a, b** as well as **3d** could also be obtained by reacting the appropriate **4** with the corresponding acetophenone in presence of catalytic amounts of *p*-toluenesulfonic acid monohydrate using the method described by Bobowski et al.[1] (Method C). In addition, the previously described **3c**[1] could be also obtained by reacting methyl isocyanate with **1c** according to the method now presented (cf. Table).

Ethyl-, phenyl-, 4-chlorophenyl and 1-naphthylisocyanates react similarly with **1a, b** affording the corresponding *N*-ethyl- and *N*-arylbenzoxazinones **3e–l**, in good yield, which have spectral features similar to **3a–c** (cf. Table), a fact which would permit generalization of this reaction as a new route to *N*-substituted 3,4-dihydro-4-phenacyl-2*H*-1,3-benzoxazinones.

Methyl isothiocyanate reacts similarly with **1a, b** to give the 2-thione analogues **5a, b**, respectively, which can be considered as representatives of a hitherto unknown series of 3,4-dihydro-4-phenacyl-2*H*-1,3-benzoxazine-2-thiones. The structures of **5a, b** are supported by their IR spectra, which lack $\nu_{C=O}$ (carbamoyloxy) (cf. Table) and by affording **3a, b** upon oxidation with yellow mercuric oxide.

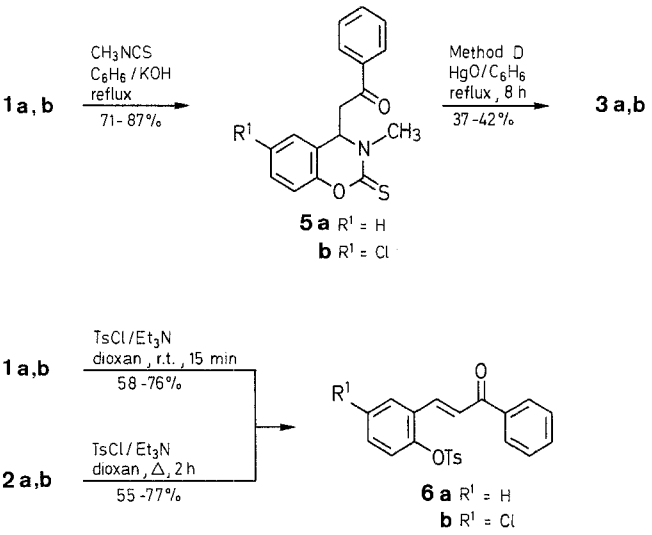
It is believed that production of the benzoxazinones **3** from chalcones proceeds through the intermediate formation of an open chain carbamate, which undergoes spontaneously intramolecular cyclization. Ring closure is promoted by the strong catalytic effect of the alkali hydroxide and the withdrawing power of the α,β-unsaturated carbonyl moiety, along with the driving force of oxazinone cyclization. This view is supported by the fact that **3a, b** are readily produced from the open chain carbamates **2a, b** using the presented procedure (Method B). The carbamates **2a, b** are obtained by treating **1a, b** with methyl isocyanate in presence of triethylamine.

Table. Compounds **2**, **3**, **5** and **6** Prepared

Product	Yield (%) (Reaction Time)	mp (°C)[a] (solvent)[b]	Molecular Formula[c]	IR (KBr)[d] (cm^{-1})				UV (CH_3OH)[e]	^{1}H-NMR ($CDCl_3$/TMS)[f], δ			
				$\nu_{C=O}$ (ketone)	$\nu_{C=O}$ (carbamoyl)	ν_{NH}	δ_{CH-CH_2}	λ_{max} (nm) (log ε)	CH[g] (1H)	CH_2[h] (2H)	CH_3 (s, 3H)	H_{arom}
2a	85 (40 min)	107–109 (A)	$C_{17}H_{15}NO_3$ (281.3)	1650	1722	3400	970					
2b	79 (3 h)	150–152 (B)	$C_{17}H_{14}ClNO_3$ (315.7)	1670	1712	3200	955					
3a	54 (1 h)	152–154 (B)	$C_{17}H_{15}NO_3$ (281.3)	1678	1710	–	–	244 (4.10)	5.12	3.38	3.12	7.00–7.87 (*m*, 9H)
3b	63 (40 min)	196–198 (D)	$C_{17}H_{14}ClNO_3$ (315.7)	1675	1720	–	–	243 (4.13)	5.09	3.43	3.12	7.00–7.96 (m, 8H)
3c				1668	1700	–	–	256 (4.19)	5.12	3.38	2.35 3.10	7.00–7.90 (m, 8H)
3d	81 (1 h)	181–183 (D)	$C_{18}H_{16}ClNO_3$ (329.8)	1672	1710	–	–	256 (4.19)	5.08	3.37	2.40	6.93–7.83 (m, 7H)
3e	68 (2 h)	87–88 (E)	$C_{18}H_{17}NO_3$ (295.3)	1675	1705	–	–					
3f	76 (4 h)	122–124 (B)	$C_{18}H_{16}ClNO_3$ (329.8)	1675	1712	–	–					
3g	92 (5 min)	173–175 (B)	$C_{22}H_{17}NO_3$ (343.4)	1675	1708	–	–	243 (4.20)	5.54	3.55		7.00–7.82 (m, 14H)
3h	69 (5 min)	165–166 (D)	$C_{22}H_{16}ClNO_3$ (377.8)	1680	1710	–	–		5.51	3.58		7.04–7.90 (m, 13H)
3i	91 (5 min)	198–200 (D)	$C_{22}H_{16}ClNO_3$ (377.8)									
3j	85 (30 min)	211–213 (D)	$C_{22}H_{15}Cl_2NO_3$ (412.3)	1675	1720	–	–		5.50	3.67		7.04–7.86 (m, 12H)
3k	90 (1 h)	189–191 (D)	$C_{26}H_{19}NO_3$ (393.4)									
3l	75 (3 h)	186–188 (D)	$C_{26}H_{18}ClNO_3$ (427.9)									
5a	71 (5 h)	119–121 (B)	$C_{17}H_{15}NO_2S$ (297.4)	1670	–	–	–					
5b	87 (8 h)	146–147 (B)	$C_{17}H_{14}ClNO_2S$ (331.8)	1675	–	–	–					
6a	76 (15 min)	114–115 (C)	$C_{22}H_{18}O_4S$ (378.4)									
6b	58 (15 min)	152–154 (C)	$C_{22}H_{17}ClO_4S$ (411.9)									

[a] Uncorrected, measured with a Büchi-510 apparatus.
[b] Solvents for recrystallization: A = benzene/petroleum ether (60–80 °C), B = benzene, C = ethanol, D = toluene, E = petroleum ether (60–80 °C).
[c] Satisfactory microanalyses obtained: C, H, N, Cl, S ± 0.4; except for **2a** (C −0.50), **3d** (Cl −0.63), **3i** (N −0.56), and **3l** (C +0.42).
[d] Recorded on a Beckman 4220 Infrared spectrophotometer.
[e] Measured using a Varian 634 UV spectrophotometer.
[f] Obtained on a Varian EM-360 60 MHz NMR spectrometer.
[g] Triplet with partially split middle peak.
[h] Partially split 3 peaks.

The IR spectra of **2a, b** show ν_{NH} and $\nu_{C=O}$ (ketonic and carbamoyloxy), as well as bands due to *trans* ethylenic out-of-plane hydrogen deformations (cf. Table). The carbamates are cleaved readily with *p*-toluenesulfonyl(tosyl) chloride under base catalysis to give the corresponding sulfonates **6a, b** through a facile transesterification process. The latter are identical with the products obtained by reacting the acid chloride with the parent chalcones.



Reaction conditions and characterization data of the products are shown in the Tables.

3-Alkyl- and 3-Aryl-3,4-dihydro-4-phenacyl-2*H*-1,3-benzoxazin-2-ones 3: General Procedure:

Method A (from 2-hydroxychalcones **1**): A mixture of the 2-hydroxychalcones **1a, b** or **c** (10 mmol) and the appropriate alkyl or aryl isocyanate (15 mmol) in dry benzene (25 mL) containing a catalytic amount of solid KOH (100 mg, ≈ 1.5 mmol) is refluxed for the time given in the Table and left to cool. The solid product formed is filtered, and recrystallized from the appropriate solvent (see Table) to give the corresponding benzoxazinones **3**.

The products, exemplified by **3a–d**, give 2,4-dinitrophenylhydrazone derivatives using the method described by Parrick and Rasburn.[4]

Method B (from 2-(*N*-methylcarbamoyloxy)chalcones **2**): A solution of the 2-(*N*-methylcarbamoyloxy)chalcone **2a** or **b** (see below) (10 mmol) in dry benzene (25 mL) containing a catalytic amount of solid KOH (100 mg, ≈ 1.5 mmol) is refluxed for 2 h, then allowed to cool. The separated product is filtered and recrystallized to give **3a** (50%) or **3b** (59%), which proved to be identical with the products obtained according to Methods A and C.

Method C (from 3,4-dihydro-4-hydroxy-3-methyl-2*H*-1,3-benzoxazin-2-ones **4**): A solution of the 4-hydroxybenzoxazinone **4a** or **b** (10 mmol) and the appropriate acetophenone (10 mmol) in dry benzene (50 mL) containing a catalytic amount of $TsOH \cdot H_2O$ (100 mg, ≈ 0.5 mmol) is refluxed for 2 h using a Dean-Stark apparatus. The reaction mixture is concentrated and allowed to cool. The solid product formed is filtered and recrystallized from the appropriate solvent (see Table) to give **3a** (86%), **3b** (74%), **3c** (78%) or **3d** (85%).

Compounds **3a–d** prepared by this method proved to be identical with the products obtained according to Methods A and B.

Method D (from 3,4-dihydro-3-methyl-4-phenacyl-2*H*-1,3-benzoxazine-2-thiones **5**): A mixture of **5a** or **b** (see below) (7 mmol) and yellow mercuric oxide (4 g) in dry benzene (25 mL) is refluxed for 8 h, then filtered while hot. The solid residue is extracted with boiling benzene (2 × 25 mL) and the combined benzene solution is concentrated to ca. 15 mL and allowed to cool. The product obtained is filtered and proved to be **3a** (42%) or **3b** (37%).

2-(*N*-Methylcarbamoyloxy)chalcones 2:
A solution of the chalcone **1a** or **b** (10 mmol) and methyl isocyanate (1.1 mL, 15 mmol) in dry benzene (25 mL) containing Et_3N (2–3 drops) is refluxed for the time given in the Table, concentrated to ca. 15 mL, and allowed to cool. In the case of **1b**, the solid formed is filtered and recrystallized from benzene to give **2b**. In the case of **1a**, petroleum ether (60–80 °C; 15 mL) is added to the reaction mixture, and the separated solid product is filtered and recrystallized from benzene/petroleum ether (60–80 °C) to give **2a**.

3,4-Dihydro-3-methyl-4-phenacyl-2*H*-1,3-benzoxaine-2-thiones 5:
The thiones **5a, b** are prepared according to Method A above by reacting the appropriate chalcone with methyl isothiocyanate.

2-Tosyloxychalcones 6:
From **1** with Tosyl Chloride: A solution of tosyl chloride (2.9 g, 15 mmol) in dioxan (10 mL) is added dropwise to a stirred solution of chalcone **1a** or **b** (10 mmol) and Et_3N (2.0 mL, 15 mmol) in dioxan (10 mL) at room temperature (25 °C). After the addition is complete, stirring is continued for an additional 15 min. The reaction mixture is poured into ice-cold water (200 mL), and allowed to stand overnight. The solid product formed is filtered, dried *in vacuo* and recrystallized from the proper solvent (see Table) to give straw yellow crystals of **6a** or **b**.

From 2 with Tosyl Chlorid: A solution of tosyl chloride (2.3 g, 12 mmol) in dioxan (10 mL) is added to a mixture of the carbamate **2a** or **b** (10 mmol) and Et_3N (2.0 mL, 15 mmol) in dioxan (10 mL). The reaction mixture is heated on a steam bath for 2 h and allowed to cool. The separated solid is removed, and the filtrate is poured into ice-cold water (200 mL). The separated product is filtered and crystallized as above to give **6a** (55%) or **6b** (77%).

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