Synthesis of Some New Spiro(pyran-4,2'-benzoxazole) Derivatives

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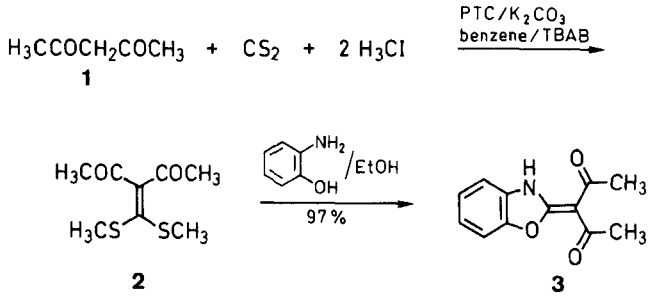
Received 25 May 1993

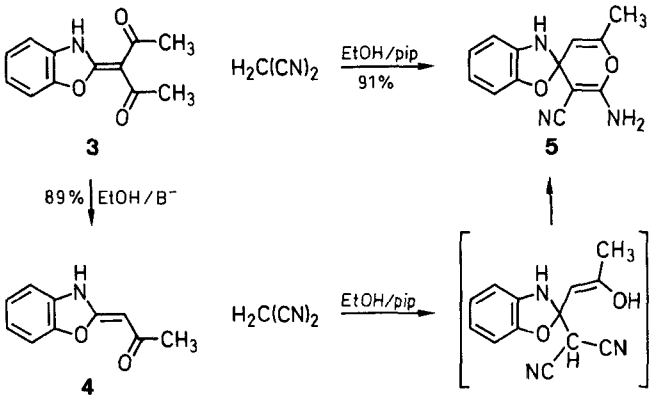
Ketene *S,S*-acetal **2** reacts with 2-aminophenol to afford 2-(1-acetyl-2-oxopropylidene)benzoxazole (**3**) which was allowed to react with a variety of active methylenes having an α-cyano or α-keto group to give spiro[pyran-4,2'-benzoxazole] derivatives **5–12**. Compound **3** also reacts with bromomalononitrile to afford spiro[3,3-diacetyl-2,2-dicyanocyclopropane-1,2'-benzoxazole] **13** through a nucleophilic addition and cyclization.

The synthesis of ketoketene[1] or cyanoketene *S,S*-acetals[2] as well as heterocyclic ketene *N,N*-[3–9] or *N,S*-acetals[5,10–14] has attracted considerable attention as these compound have been used as versatile starting materials for the synthesis of a wide variety of fused heterocycles.

In an extension of our recent studies[15,16] on the application of cyanoketene *S,S*-acetals in heterocyclic synthesis using phase transfer conditions (PTC), we report here the synthesis of some new spiro heterocyclic systems starting with heterocyclic ketene *N,O*-acetal[17] **3**. Compound **3** was prepared starting with 2-acetyl-2-oxopropylidene *S,S*-acetal **2** which was obtained via reaction of acetylacetone, CS_2 and two moles of methyl iodide in a one-pot reaction using PTC [K_2CO_3/benzene/tetrabutylammonium bromide (TBAB)] in almost 100% yield. Compound **2** was then reacted with 2-aminophenol in refluxing absolute ethanol for about 24 h to give compound **3**. This reaction was assumed to go through a nucleophilic attack of both –OH and $-NH_2$ groups at the ethylenic bond with elimination of two moles of methyl mercaptan.



2-(1-Acetyl-2-oxopropylidene)benzoxazole (**3**) was then allowed to react with malononitrile in refluxing ethanol in presence of a piperidine base where spiro[2-amino-3-cyano-6-methylpyran-4,2'-benzoxazole] (**5**) was precipitated after heating for about 30 minutes. The reaction pathway was assumed to follow a preliminary hydrolysis of one of the acetyl groups followed by a nucleophilic addition of malononitrile at the ethylenic bond followed by cyclization. This proposed mechanism was confirmed by a two-step reaction where compound **3** was hydrolysed by boiling in ethanol in presence of piperidine or sodium methoxide into the intermediate product 2-(2-oxopropylidene)benzoxazole (**4**) which was refluxed in boiling ethanol with malononitrile in the presence of a catalytic amount of piperidine to afford compound **5**.



Compound **3** was then reacted with a variety of active methylene compounds including acetylacetone, ethyl acetoacetate, cyanoacetamide, cyanoacetohydrazide and 3-methyl-1-phenylpyrazol-5-one in refluxing ethanol containing piperidine as a catalyst where in each reaction a preliminary hydrolysis of one of the acetyl groups was effected followed by a nucleophilic addition of the formed carbanion at the ethylenic bond and cyclization to give

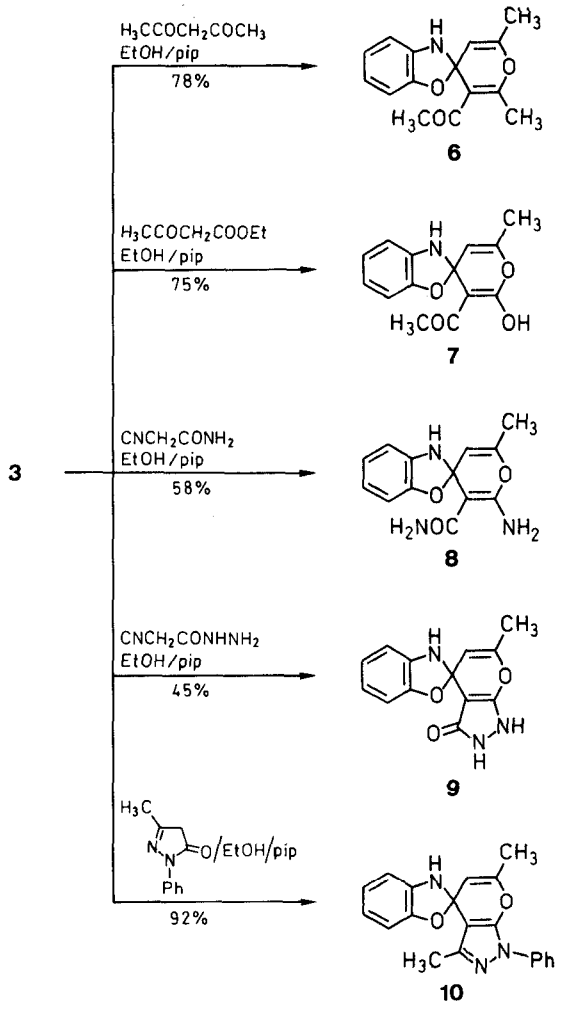


Table. Analytical and Spectral Data of the Reported New Compounds[a]

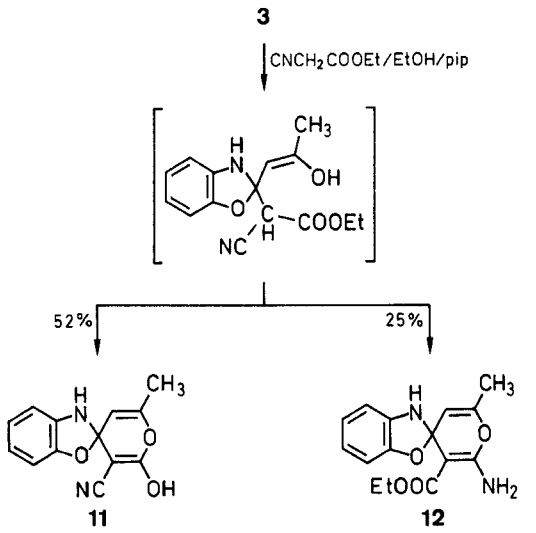
Product	Yield (%)	mp (°C)[b]	IR (Nujol) ν (cm^{-1})[c]	^1H NMR[d]
3	97	129–130	3450 (NH), 3050 (CH_{arom}), 2970–2920 (CH_{aliph}), 1660 (C=O), 1525 (C=C)	$CDCl_3$: 11.20 (br, 1H, NH), 7.80–7.20 (m, 4H, CH_{arom}), 2.30–2.10 (s, 6H, $2CH_3$)
4	89	70	3430 (NH), 3050 (CH_{arom}), 2970 (CH_{aliph}), 1650 (C=O), 1550 (C=C)	$CDCl_3$: 11.20 (br, 1H, NH), 8.70–8.20 (m, 4H, CH_{arom}), 5.10 (s, 1H, =CH), 3.20 (s, 3H, CH_3)
5	91	212–213	3490, 3250, 3100 (NH, NH_2), 3030 (CH_{arom}), 2980 (CH_{aliph}), 2210 (CN), 1660 (C=O), 1560 (C=C)	$CDCl_3$: 8.80–8.60 (br, 1H, NH), 7.50–7.20 (m, 4H, CH_{arom}), 6.90–6.70 (br, 2H, NH_2), 5.90 (s, 1H, =CH), 2.30 (s, 3H, CH_3)
6	78	202	3420 (NH), 3050 (CH_{arom}), 2970 (CH_{aliph}), 1640 (C=O), 1560 (C=C)	DMSO: 9.30–9.10 (br, 1H, NH), 7.80–7.10 (m, 4H, CH_{arom}), 5.90 (s, 1H, =CH), 2.40 (s, 3H, $COCH_3$), 2.20 (s, 6H, $2CH_3$)
7	75	225	3500 (OH), 3420 (NH), 3030 (CH_{arom}), 2970 (CH_{aliph}), 1670 (C=O), 1550 (C=C)	DMSO: 9.80 (s, 1H, NH), 9.60 (s, 1H, OH), 7.80–7.20 (m, 4H, CH_{arom}), 6.10 (s, 1H, =CH), 2.30–2.20 (d, 6H, $2CH_3$)
8	58	120–121	3450 (NH), 3300, 3250, 3100 (NH_2, $CONH_2$), 3030 (CH_{arom}), 2990, 2980 (CH_{aliph}), 1640 (C=O), 1560 (C=C)	$CDCl_3$: 9.20 (s, 1H, NH), 7.50–7.30 (m, 5H, CH_{arom} + 1H, =CH), 6.30–6.00 (br, 2H, NH_2), 5.80–5.65 (br, 2H, $CONH_2$), 2.40 (s, 3H, CH_3)
9	45	175–176	3450, 3400 (NH), 3030 (CH_{arom}), 2970 (CH_{aliph}), 1630 (C=O), 1520 (C=C)	DMSO: 8.90 (s, 1H, NH), 8.40 (d, 2H, 2NH), 8.10– 7.80 (m, 4H, CH_{arom}), 6.90 (s, 1H, =CH), 2.50 (s, 3H, CH_3)
10	92	181–182	3450 (NH), 3050 (CH_{arom}), 2970 (CH_{aliph}), 1600 (C=N), 1520 (C=C)	DMSO: 9.10 (s, 1H, NH), 7.90–7.20 (m, 9H, CH_{arom}), 6.80 (s, 1H, =CH), 2.80 (s, 3H, CH_3-pyrazole), 2.30 (s, 3H, CH_3-pyran)
11	52	295–296	3500 (OH), 3420 (NH), 3050 (CH_{arom}), 2980 (CH_{aliph}), 2210 (CN), 1560 (C=C)	$CDCl_3$: 8.90 (s, 1H, NH), 8.60 (s, 1H, OH), 7.70–7.30 (m, 4H, CH_{arom}), 6.70 (s, 1H, =CH), 2.60 (s, 3H, CH_3)
12	25	220	3450, 3300, 3200 (NH, NH_2), 3050 (CH_{arom}), 2970 (CH_{aliph}), 1720 (C=O), 1560 (C=C)	$CDCl_3$: 9.30 (s, 1H, NH), 7.80–7.40 (m, 4H, CH_{arom}), 6.80 (s, 2H, NH_2), 6.60 (s, 1H, =CH), 3.60–3.30 (q, 2H, CH_2), 2.30 (s, 3H, CH_3), 1.30–1.00 (t, 3H, CH_3-ester)
13	82	167–169	3450 (NH), 3050 (CH_{arom}), 2980 (CH_{aliph}), 2220–2210 (2CN), 1710 (C=O), 1520 (C=C)	DMSO: 9.60 (s, 1H, NH), 8.00–7.50 (m, 4H, CH_{arom})

[a] Satisfactory microanalysis obtained: C ± 0.4, H ± 0.3, N ± 0.3%.
[b] Not corrected.
[c] Measured on a Pye-Unicam SP3-100 infrared Spectrophotometer.
[d] Measured on Varian EM 360 A Spectrometer using TMS as internal standard.

the desired spiro heterocycles, namely: spiro[3-acetyl-2,6-dimethylpyran-4,2′-benzoxazole] **(6)**, spiro[3-acetyl-2-hydroxy-6-methylpyran-4,2′-benzoxazole] **(7)**, spiro [2-amino-3-carboxamido-6-methylpyran-4,2′-benzoxazole] **(8)**, spiro[6-methylpyrazolo[3,4-*b*]pyran-4,2′-benzoxazol-3(1*H*,2*H*)-one] **(9)**, and spiro[3,6-dimethyl-1-phenylpyrazolo[3,4-*b*]pyran-4,2′-benzoxazole] **(10)**.

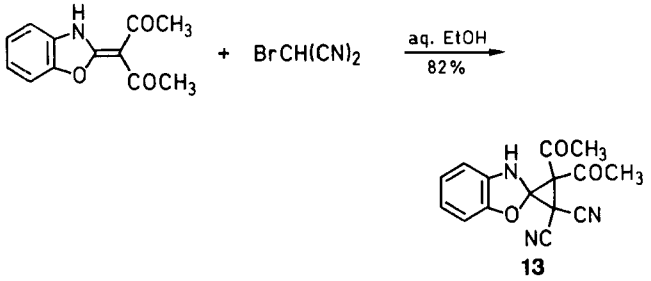
In the case of reaction of compound **3** with cyanoacetohydrazide a clear evolution of NH_3 gas was observed and the analytical and spectral data (cf. Table 1) of the obtained product revealed that a fused pyrazolone ring was formed most probably via a nucleophilic attack of the $-NHNH_2$ group at the C–NH_2 linkage of the γ-pyran nucleus followed by cyclization into compound **9**.

The reaction of compound **3** with ethyl cyanoacetate, under the same experimental conditions gave two compounds. The major one was precipitated on heating and proved to be spiro[3-cyano-2-hydroxy-6-methylpyran-4,2′-benzoxazole] **(11)**, another product was separated from the mother liquor and was identified as spiro[2-amino-3-ethoxycarbonyl-6-methylpyran-4,2′-benzoxazole] **(12)**. The reaction pathway is thus assumed to involve an intramolecular nucleophilic attack of the –OH group in the intermediate compound at either the ethoxycarbonyl or the cyano groups respectively to give compounds **11** or **12**, respectively.



When compound **3** was stirred with bromomalononitrile in aqueous ethanol at room temperature without any catalyst, spiro[3,3-diacetyl-2,2-dicyanocyclopropane-1,2′-benzoxazole] **(13)** was obtained. This is a result of a nucleophilic addition of bromomalononitrile at the ethylenic bond followed by HBr elimination and cyclization. Similar reactions were reported where 3,3-dialkyl- and 3-aryl-2-ethoxycarbonyl-1,1,2-tricyanocyclopropanes or

3-aryl-2-carboxamido-1,1,2-tricyanocyclopropanes were obtained from alkyl- and arylidenecyanoesters or arylidenecyanoacetamides[18] and bromomalononitrile under similar reaction conditions.



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All melting points were determined on a Kofler melting point apparatus and were uncorrected. IR spectra were obtained on a Pye-Unicam SP3-100 infrared spectrophotometer. ^{1}H NMR spectra were obtained on a Varian EM 360 A at 60 MHz using TMS as an internal standard. The elemental analyses were carried out on an elemental analyzer model 240 C.

2-[Di(methylthio)methylene]pentane-2,4-dione (2):

An equimolar mixture (0.05 mol) of acetylacetone and CS_2 in 70 mL benzene was treated with 7 g of anhydr. K_2CO_3. The formed dianionic ambident compound was then treated with 0.1 mol of methyl iodide and a catalytic amount of tetrabutylammonium bromide (TBAB, 3 mmol). The reaction mixture was stirred for about 3 h at 60 °C and the benzene layer was then separated by filtration, washed throughly with water, dried ($MgSO_4$) and evaporated in vacuo. The residue was washed with light petroleum (40–60 °C) and collected by filtration as cubic colorless crystals, mp 61 °C, yield 98%.

2-(1-Acetyl-2-oxopropylidene)benzoxazole (3):

A mixture of ketene *S,S*-acetal **2** (4.0 mmol) and 2-aminophenol (4.1 mmol) was refluxed in abs EtOH (25 mL) for 24 h. On cooling, the precipitate was filtered off and crystallized from abs EtOH into colorless needles.

2-(2-Oxopropylidene)benzoxazole (4):

Method A:

A mixture of compound **3** (10 mmol) and NaOMe (1 g of Na in 30 mL of MeOH) was refluxed for 4 h, water (20 mL) was then added and the mixture was extracted with $CHCl_3$ (3 × 50 mL). The organic extract was dried (Na_2SO_4), and evaporated to give a solid precipitate which was recrystallized from EtOH as yellow crystals.

Method B:

A mixture of compound **3** (0.01 mol) and piperidine (1 mL) in EtOH (30 mL) was refluxed for 1 h, and the mixture was concentrated to half its volume. On cooling, the precipitated solid was filtered off and recrystallized from EtOH.

Spiro[pyran-4,2′-benzoxazole] 5–10es; General Procedure:

Compound **3** (0.01 mol) and piperidine (1 mL) were added to a stirred suspension of the appropriate active methylene reagent (0.01 mol) in EtOH (50 mL). The reaction mixture was refluxed over different periods of time and then allowed to cool, the resulting solid was collected by filteration and recrystallized from the proper solvent.

2-Amino-3-cyano-6-methylspiro[pyran-4,2′-benzoxazole] (5):

The reaction mixture was refluxed for 1 h, the solid product was filtered off and recrystallized from EtOH as greenish yellow crystals.

3-Acetyl-2,6-dimethylspiro[pyran-4,2′-benzoxazole] (6):

The reaction mixture was refluxed for 2 hrs., the solid product was filtered off and recrystallized from MeOH as yellow crystals.

3-Acetyl-2-hydroxy-6-methylspiro[pyran-4,2′-benzoxazole] (7):

The reaction mixture was refluxed for 2 h, the solid product was filtered off and recrystallized from EtOH as pale brown crystals.

2-Amino-3-carboxamido-6-methylspiro[pyran-4,2′-benzoxazole] (8):

The reaction mixture was refluxed for 2 h, then concentrated to half its volume and left to cool. The solid product obtained was filtered off and recrystallized from aq EtOH giving colorless crystals.

6-Methylspiro[pyrazolo[3,4-b]pyran-4,2′-benzoxazole]-3(1*H*,2*H*)-one (9):

This compound was synthesized in analogy to the method given above and was recrystallized from $CHCl_3$ as white crystals.

3,6-Dimethyl-1-phenylspiro[pyrazolo[3,4-b]pyran-4,2′-benzoxazole] (10):

The reaction mixture was refluxed for 1 h, the solid product was filtered off and recrystallized from EtOH as orange crystals.

3-Cyano-2-hydroxy-6-methylspiro[pyran-4,2′-benzoxazole] (11) and 2-Amino-3-ethoxycarbonyl-6-methylspiro[pyran-4,2′-benzoxazole] (12):

The reaction mixture was refluxed for 2 h, the solid product was filtered off and recrystallized from EtOH to give compound **11** as white crystals. The filtrate was concentrated, left to cool and poured into ice-cold water. The solid product was filtered off and recrystallized from dioxane to give compound 12 as yellow crystals.

3,3-Diacetyl-2,2-dicyanospiro[cyclopropane-1,2′-benzoxazole] (13):

A mixture of compound **3** (0.01 mol) and bromomalononitrile (0.01 mol) was dissolved in (30 mL) aq EtOH (95%). The reaction mixture was stirred at r.t. for 2 h, the solid product was filtered off and recrystallized from EtOH as white crystals.

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