Synthesis of 8-Aryl-6-Thioxo-6H-1,9-Dioxa-7-Aza-Cyclopenta[a]Naphthalen-3-One under Solvent-Free Conditions at Ambient Temperature

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ABSTRACT

We report a green and efficient method for the synthesis of 8-aryl-6-thioxo-6H-1,9-dioxa-7-aza-cyclopenta[a]naphthalen-3-one from the condensation of ammonium thiocyanate and acid chlorides with 7-hydroxy-3-coumaranone in the presence of catalytic amounts of N-methylimidazole under solvent-free conditions at ambient temperature. This new protocol offers advantages, such as mild reaction conditions, short reaction time, easy work-up, and use of an inexpensive and nontoxic catalyst, high yields of biological active products and does not involve any hazardous solvent. This prompted us to establish a novel oxazine ring formation method to find promising bioactive oxazine compounds. They are found to have exhibit diverse pharmacological properties.

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8-Aryl-6-thioxo-6H-1,9-dioxa-7-aza-cyclopenta[a]naphthalen-3-one; 7-hydroxy-3-coumaranone; acid chlorides; ammonium thiocyanate; N-methylimidazole; solvent-free conditions

Introduction

1,3-oxazine derivatives have found versatile applications in the biological fields as anti-bacterial and cancer screening agents. They were also found to have antifungal action and are used as herbicides. The thio derivatives of pyrano-1,3-benzoxazine have also shown anti-inflammatory and antipyretic properties. Multi-component reactions (MCRs) have been frequently used by synthetic chemists as a facile means to generate molecular diversity from bifunctional substrates that react sequentially in an intramolecular fashion.

The synthesis of chromeno[3,4-e][1,3]oxazine is performed by condensation of 4-hydroxycoumarins with azomethines and aldehydes. Reaction between cyclic β-diketones and 1-chloroalkyl isocyanates leading to the formation of carbofused 1,3-oxazines. Also, synthesis of [1,3]oxazine derivatives has already been reported and this synthesis used a procedure first described by Khalilzadeh et al., in which they synthesized a series of arylated bi- and tri-cyclic thioheterocycles via the N-methylimidazole-catalyzed reaction of phenol and 1- and 2-naphthols with a...
series of acid chlorides and ammonium thiocyanate. Although many useful and reliable methods for preparation of 1,3-oxazines have been reported in the literature, many of these procedures have significant drawbacks such as low yields of the products, long reaction times, and harsh reaction conditions. Thus, in continuation of our investigations on the development of new routes in organic synthesis, we have developed a mild, high efficient, simple work-up, one-pot selective method for synthesis of biologically active 8-aryl-6-thioxo-6H-1,9-dioxa-7-aza-cyclopenta[a]naphthalen-3-one in the presence of catalytic amounts of N-methylimidazole under solvent-free conditions at ambient temperature with excellent yield. The obtained products may be also interesting in different application fields or as starting material in the synthesis of new compounds. This prompted us to establish a novel oxazine ring formation method to find promising bioactive oxazine compounds. As part of our current studies on the development of new routes in organic synthesis,19,20 in this study, we have used this procedure to synthesis another class of arylated cyclic thionoheterocycles via a three-component condensation reaction of 7-hydroxy-3-coumaranone and acid chlorides with ammonium thiocyanate in the presence of N-methylimidazole as catalyst.

**Experimental**

**General**

Melting points were determined with an Electrothermal 9100 apparatus and were uncorrected. Elemental analysis was performed using a Heraeus CHN–O–Rapid analyzer. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. IR spectra of selected compounds were recorded on a Shimadzu IR-470 spectrometer in KBr disks. $^1$H and $^{13}$C NMR spectra were obtained on a Bruker DRX-300 Avance spectrometer in DMSO-$d_6$ using TMS as internal standard. The chemicals used in this work were purchased from Fluka (Buchs, Switzerland) and were used without further purification.

**General experimental procedure for the synthesis of 8-aryl-6-thioxo-6H-1,9-dioxa-7-aza-cyclopenta[a]naphthalen-3-one (4a–f)**

Acid chloride (2 mmol) was added to ammonium thiocyanate (0.15 g, 2 mmol) in a 50 mL flask at room temperature via a syringe. The reaction mixture was stirred in a water bath at about 90°C for 5 min. Then 7-hydroxy-3-coumaranone (2 mmol) was added at this temperature. The reaction mixture was allowed to cool to room temperature. Finally, N-methylimidazole (0.082 g; 1 mmol) as catalyst was added via a syringe. The resulting mixture was stirred at room temperature for 1 h. The progress of the reaction was monitored by TLC. After completion of the reaction, water (15 mL) was added over 5 min to the reaction mixture. The resulting precipitate was filtered off, to give a pure product.

**The analytical and spectroscopic data for the unknown compounds**

**8-(4-Nitrophenyl)-6-thioxo-6H-1,9-dioxa-7-aza-cyclopenta[a]naphthalen-3-one (4a)**

Yellow powder; m.p. 174–176°C; IR (KBr) ($\nu_{\text{max}}$ cm$^{-1}$): 1654, 1580, 1386, 1264, 1107; $^1$H NMR: $\delta$ 4.64 (2H, s, CH$_2$), 7.40 (1H, d, $^3$J$_{HH}$ = 6.9 Hz, Ar), 7.45 (1H, d, $^3$J$_{HH}$ = 6.9 Hz, Ar), 8.05 (2H, d, $^3$J$_{HH}$ = 8 Hz, 2CH of C$_6$H$_4$NO$_2$), 8.24 (2H, d, $^3$J$_{HH}$ = 8 Hz, 2CH of C$_6$H$_4$NO$_2$) ppm; $^{13}$C NMR: $\delta$ 76.6, 114.3, 124.8, 125.1, 126.4, 130.3, 131.5, 132.8, 137.8, 141.4, 151.4, 168.3, 177.0, and 198.1 ppm.; EIMS: 340 (M$^+$, 10 ); Anal. Calcd. for C$_{16}$H$_8$N$_2$O$_5$S: C, 56.47; H, 2.37; N, 8.23; found: C, 56.55; H, 2.44; N, 8.35%.
8-(4-Chlorophenyl)-6-thioxo-6H-1,9-dioxa-7-aza-cyclopenta[a]naphthalen-3-one (4b)
Yellow powder; m.p. 203–205 °C; IR (KBr) (νmax cm⁻¹): 1652, 1607, 1264, 1108; ¹H NMR: δ 4.82 (2H, s, CH₂), 7.41 (1H, d, JHH = 6.9 Hz, Ar), 7.52 (1H, d, JHH = 6.9 Hz, Ar), 6.55 (2H, d, JHH = 8 Hz, 2CH of C₆H₄Cl), 7.67 (2H, d, JHH = 8 Hz, 2CH of C₆H₄Cl) 6.48–7.70 ppm; ¹³C NMR: δ 76.6, 114.3, 126.4, 129.8, 130.5, 131.9, 132.5, 133.1, 139.3, 140.7, 159.3, 168.2, 177.0, and 198.7 ppm.; EIMS: 329 (M⁺, 6 ); Anal. Calcd. for C₁₄H₈ClNO₃S: C, 58.28; H, 2.45; N, 4.25; found: C, 58.37; H, 2.52; N, 4.35%.

8-(2,4-Dichlorophenyl)-6-thioxo-6H-1,9-dioxa-7-aza-cyclopenta[a]naphthalen-3-one (4c)
Yellow powder; m.p. 227–229 °C; IR (KBr) (νmax cm⁻¹): 1652, 1608, 1270, 1108; ¹H NMR: δ 4.84 (2H, s, CH₂), 6.48–6.57 (3H, m, 3CH of aromatic), 7.40–7.63 (2H, m, 2CH of aromatic) ppm; ¹³C NMR: δ 76.6, 114.3, 126.4, 128.5, 128.9, 129.3, 129.6, 131.6, 132.4, 132.6, 133.5, 136.2, 147.3, 168.2, 177.1, and 198.3 ppm.; EIMS: 363 (M⁺, 3); Anal. Calcd. for C₁₆H₇Cl₂NO₃S: C, 52.77; H, 1.94; N, 3.85; found: C, 52.84; H, 2.00; N, 3.84%.

8-(4-Methylphenyl)-6-thioxo-6H-1,9-dioxa-7-aza-cyclopenta[a]naphthalen-3-one (4d)
Yellow powder; m.p. 242–244 °C; IR (KBr) (νmax cm⁻¹): 1652, 1609, 1271, 1108; ¹H NMR: δ 2.06 (3H, s, CH₃), 4.65 (2H, s, CH₂), 6.52 (1H, d, JHH = 6.9 Hz, Ar), 6.55 (1H, d, JHH = 6.9 Hz, Ar), 6.46 (2H, d, JHH = 8 Hz, 2CH of C₆H₄CH₃), 7.42 (2H, d, JHH = 8 Hz, 2CH of C₆H₄CH₃) ppm; ¹³C NMR: δ 21.0, 76.6, 114.4, 124.7, 126.4, 126.9, 128.3, 129.6, 130.9, 131.4, 140.5, 143.1, 168.2, 177.0, and 198.2 ppm.; EIMS: 309 (M⁺, 5 ); Anal. Calcd. for C₁₇H₁₁NO₃S: C, 66.01; H, 3.58; N, 4.53; found: C, 66.10; H, 3.65; N, 4.60%.

2-Phenyl-6-thioxo-6H-1,9-dioxa-7-aza-cyclopenta[a]naphthalen-3-one (4e)
Yellow powder; m.p. 219–221 °C; IR (KBr) (νmax cm⁻¹): 1651, 1609, 1271, 1107; ¹H NMR: δ 4.67 (2H, s, CH₂), 6.94–7.05 (4H, m, 4CH of aromatic), 7.51–7.83 (3H, m, 3CH of aromatic) ppm; ¹³C NMR: δ 76.5, 117.6, 126.0, 126.4, 127.5, 128.4, 129.0, 129.7, 131.3, 135.2, 143.7, 168.3, 175.9, and 199.3 ppm.; EIMS: 295 (M⁺, 8 ); Anal. Calcd. for C₁₆H₉NO₃S: C, 65.07; H, 3.07; N, 4.74; found: C, 65.15; H, 3.13; N, 4.80%.

8-Methyl-6-thioxo-6H-1,9-dioxa-7-aza-cyclopenta[a]naphthalen-3-one (4f)
Yellow powder; m.p. 263–265 °C; IR (KBr) (νmax cm⁻¹): 1653, 1608, 1266, 1106; ¹H NMR: δ 2.23 (3H, s, CH₃), 4.68 (2H, s, CH₂), 7.41–7.50 (2H, m, 2CH of aromatic) ppm; ¹³C NMR: δ 32.6, 76.7, 113.7, 126.5, 126.9, 129.4, 130.5, 132.0, 168.2, 177.1, and 198.7 ppm.; EIMS: 233 (M⁺, 5 ); Anal. Calcd. for C₁₁H₂NO₃S: C, 56.64; H, 3.03; N, 6.01; found: C, 56.70; H, 3.11; N, 6.10%.

Results and discussion

Using reaction conditions similar to those previously described,¹⁸ an acid chloride 2 was reacted with ammonium thiocyanate 3 initially under solvent-free conditions at ambient temperature and then at 90 °C for 5 min prior to the addition of 7-hydroxy-3-coumaranone 1. After cooling to room temperature, N-methylimidazole as catalyst was added and the mixture was stirred for 1 h to afford the arylated cyclic thionoheterocycles 4 in excellent yields (Scheme 1 and Table 1).

N-methylimidazole is used for preparation of 8-aryl-6-thioxo-6H-1,9-dioxa-7-aza-cyclopenta[a]naphthalen-3-one. In order to establish the better catalytic activity of N-methylimidazole, we have compared the reaction using other catalysts. The results are listed in Table 2.
To find out the optimum quantity of N-methylimidazole, the reaction of ammonium thiocyanate and acid chlorides with 7-hydroxy-3-coumaranone was carried out at 25°C and under solvent-free conditions using different quantities of N-methylimidazole (Table 2).

| Entry | Catalyst/mol% | Time/min | Yield% a |
|-------|---------------|----------|----------|
| 1     | 3             | 90       | 45       |
| 2     | 5             | 70       | 60       |
| 3     | 7             | 60       | 70       |
| 4     | 10            | 60       | 91       |
| 5     | 12            | 60       | 91       |

Table 3. Optimization amount of N-methylimidazole on the reaction of condensation of ammonium thiocyanate and acid chlorides with 7-hydroxy-3-coumaranone was carried out at 25°C and under solvent-free conditions.

| Entry | Catalyst/mol% | Time/min | Yield% a |
|-------|---------------|----------|----------|
| 1     | 3             | 90       | 45       |
| 2     | 5             | 70       | 60       |
| 3     | 7             | 60       | 70       |
| 4     | 10            | 60       | 91       |
| 5     | 12            | 60       | 91       |

The structures of compounds 4a–f were deduced from elemental analysis and their IR, 1H NMR, and 13C NMR spectra. The mass spectra of compounds 4a–f are fairly similar and display molecular ion peaks. For example, the mass spectrum of compound 4a showing a molecular ion peak at m/z 340 confirmed that compound 4a is a condensation product of 7-hydroxy-3-coumaranone, 4-nitrobenzoyl chloride, and ammonium thiocyanate. The 1H NMR spectrum of 4a exhibited a sharp singlet readily recognized as arising from methylen (δ = 4.64 ppm), and along with multiplets (δ = 7.23–8.26 ppm) for aromatic protons. The 13C NMR spectrum of compound 4a...
shows 14 distinct signals consistent with the proposed structure. The IR spectrum of compound 4a also supported the suggested structure.

A tentative mechanism for this transformation is proposed in Scheme 2. It is conceivable that the reaction starts with formation of alkanoyl or aroyl isothiocyanate 5, followed by formation of the 1:1 adducts 6 and its subsequent protonation by 7-hydroxy-3-coumaranone to produce 7. Then, the positively charged ion 7 is attacked by the anion of 7-hydroxy-3-coumaranone 8. Intermediate 9 undergoes cyclization reaction and elimination of water to produce 4.

**Conclusions**

In conclusion, we have demonstrated that the thermal solvent-free green procedure in the presence of N-methylimidazole as catalyst is efficient for synthesis of 8-aryl-6-thioxo-6H-1,9-dioxo-7-aza-cyclopenta[a]naphthalen-3-one. The obtained products were prepared via a three-component reaction of ammonium thiocyanate and a series of acid chlorides with 7-hydroxy-3-coumaranone in the presence of N-methylimidazole as catalyst under solvent-free conditions at ambient temperature. This procedure has the advantage that the reaction is performed under neutral conditions and the starting material can be used without any activation or modification. The thermal solvent-free green procedures offer advantages, such as mild reaction conditions, short reaction time, easy work-up, and use of an inexpensive and nontoxic catalyst, high yields of biological active products.

**Disclosure statement**

There are no conflicts of interest.
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