Unusual reactivity of 2,3-diphenylcyclopropenone towards *N*-imidoylthioureas; facile synthesis of 3-aryl-2,5,6-triphenylpyrimidin-4(3*H*)-one (PART III)

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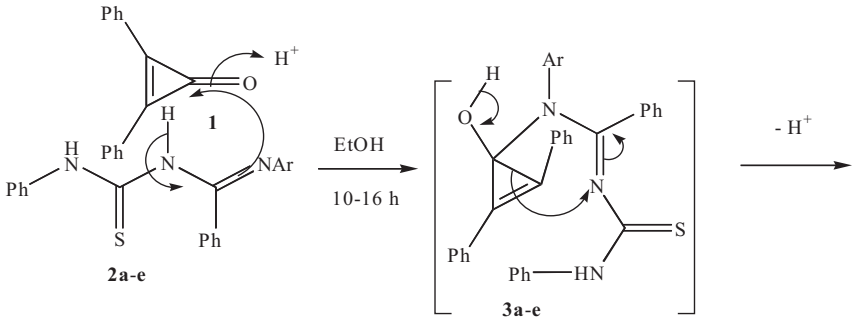
2,3-Diphenylcyclopropenone (**1**) reacts with *N*-imidoylthioureas **2a–e** to form the pyrimidin-4(3*H*)-ones **5a–e**. The reaction mechanism can be described as due to stepwise addition accompanied by elimination of phenyl isothiocyanate.

Keywords: *N*-imidoylthioureas, 2,3-diphenylcyclopropenone, stepwise mechanism, pyrimidin-4-ones

Cyclopropenones undergo several interesting cycloaddition reactions and they may be useful starting materials for a variety of compounds.[1,2] They are also reactive toward dipolar reagents and compounds having a reactive π-system.[3-5] There is systematic interest in the use of cyclopropenone chemistry to construct a wide variety of heterocycles.[6] Diphenylcyclopropenone (**1**) has been found to react with a wide range of imines and other compounds containing the C=N moiety, usually to form azacyclopentenones (pyrrolinones) *via* formal [2 + 3] cycloaddition reactions.[7-12] By contrast, the reaction of **1** with guanidine and its alkyl and/or aryl derivatives gave the corresponding 5,6-dihydropyrimidin-4(1*H*)-ones *via* a formal [3 + 3] cycloaddition reaction.[13] In general, cyclopropenones are strained ring ambident electrophiles with a tendency to form ring opened products; their reaction with nucleophiles can involve carbonyl or conjugate addition.[14,15] *N*-Imidoylthioureas have been shown limited attention in the field of heterocyclic synthesis.[16,17] The synthesis of pyridazinethiones and 1,2,4-triazolo[4,3-*b*]pyridazinethiones from the reaction of thiosemicarbazides with **1** has been described previously.[18] Moreover, we have isolated (*E*/*Z*)-3-(aroylthioureido)-2-phenylcinnamates from the reactions of *N*-substituted aroylthioureas with **1** in acetic acid. That abnormal activity was described as due to nucleophilic addition of N^3 followed by hydrolysis, ring opening and oxidation processes.[19] It has recently been reported[20] that (*E*)-N-[2-([2.2]paracyclophan-4-yl)ethylidene] methylamine-*N*-oxide reacted with **1** to produce the corresponding paracylophanyl-pyrrole-2-one. Yoshida[21] previously reported that the reaction of *N*-imidoyl sulfoximides with **1** at 150°C afforded a mixture of 1,2-disubstituted 5,6-diphenylpyrimidin-4(1*H*)-ones and *N*-(4-oxo-2-pyrrolin-5-yl) sulfoximides. On the other hand, compound **1** reacted with sulfimides to give predominately pyrimidin-4-ones.[22-24] 4-Pyrimidones were also obtained from the reaction of 2,4,5-triphenyl-3*H*-pyrrol-3-one 1-oxide with nitrones.[25]

Results and discussion

In the light of the aforementioned results, our attention turned to the reactions of 2,3-diphenylcyclopropenone (**1**) with



2-5	Ar	Yield (%)
a	4-OCH_3-C_6H_4-	80
b	4-CH_3-C_6H_4-	76
c	4-Cl-C_6H_4-	70
d	4-NO_2-C_6H_4-	60
e	C_6H_5-	74

Scheme 1 Rationale for the formation and synthesis pyridim-4(3*H*)-ones **5a–e**.

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N-imidoylthioureas **2a–e** (Scheme 1). We chose *N*-imidoyl thioureas **2a–e** having aryl groups with electron donating and withdrawing substituents on the benzene ring, in order to examine their reactivity which might affect the course of reaction. The reactions of **2a–e** with **1** were carried out in absolute ethanol at reflux temperature and afforded compounds **5a–e** in 60–80% yields together with small amounts of phenyl isothiocyanate in nearly 5% (Scheme 1). The structure proof of **5a–e** was based upon the mass, ^{1}H NMR, ^{13}C NMR and IR spectra as well as elemental analyses. For example, the reaction of compound **1** with **2a**, for 10 h, furnished yellow crystals of **5a** in 80% yield (Scheme 1). Mass spectrometry and elemental analysis proved the molecular formula of **5a** as $C_{29}H_{22}N_2O_2$. The IR spectrum did not reveal any absorption assigned to the presence of NH, CS, or OH groups. However, a sharp band appeared at $\nu = 1695$ cm^{-1} due to the presence of a carbonyl group. The aromatic protons resonated in the ^{1}H NMR spectrum of **5a** as two double–doublets and two multiplets, respectively corresponding to the *p*-methoxyphenyl group and the other three phenyl groups. The ^{13}C DEPT 135/90 spectrum of **5a** supported the ^{1}H NMR spectroscopic data by the appearance of the positive amplitude appearance of only 11 aromatic-CH signals; in eight of them each signal constitutes two carbons (see the Experimental). Distinctive signals appeared in the ^{13}C NMR spectrum of **5a** at δ_C 51.0, 124.0, 132.0, 145.9, 150.9, 162.1 and 168.8 corresponding to O*C*H$_3$, *C*-5, *N*–Ar–*C*, *C*-6, OMe–Ar–*C*, *C*-2 and *C*-4, respectively.

In the case of **5d**, the ^{1}H NMR spectrum revealed the most deshielded aromatic protons as two double–doublets at δ_H 8.10 and 7.80 (J = 8.0, 1.2 Hz) corresponding to the phenyl group connected to the nitro group. Additionally, the nitrophenyl carbon signals appeared at different magnetic fields at δ_C 120.0 (2CH), 124.0 (2CH), 140.2 (NO_2–*C*–Ph), and 143.8 (N–Ph–*C*). Moreover, COSY H H and C H spectra of **5a** and **5d** yielded some distinctive δ values as given in Fig. 1.

The structure of the obtained products (Scheme 1) excluded formal [2 + 3] cycloaddition pathways such as that proposed by Eicher.[7-12] The reaction mechanism can be simply described as due to nucleophilic attack of the amidine group on the cyclopropenone **1** to form **3a–e** (Scheme 1). Subsequently, further nucleophilic addition of the strained cyclopropenone on the positively nitrogen occurred to afford the unstable intermediates **4a–e** (Scheme 1). In a fast step, intermediates **4a–e** quickly lose a molecule of phenyl isothiocyanate accompanied by extrusion of a hydride ion to form the stable heterocyclic compounds **5a–e**. It is noteworthy that Eicher[9] and recently Aly[19] have isolated many oxidised products during the reaction of benzylidene azines with **1**. Moreover, aerial oxidation of *N*-phenylthioformamide (**6**) occurs[26] which may be catalysed under the reaction conditions (Scheme 1). This may also explain the low yield of the resulting phenyl isothiocyanate.

In the last few years, substituted pyrimidinone and pyrimidinedione derivatives have shown selective antitumor,[26] antiviral,[27] antitubercular,[28] and antifungal activity.[29] From the aforesaid follows the importance of our mode of synthesis, since the products formed from readily available starting materials. Moreover, these products can be expected to have biological and pharmaceutical activities.

Experimental

All melting points were recorded on a Gallenkamp apparatus. The IR spectra were obtained on Shimadzu 470 spectrophotometer using potassium bromide pellets. The ^{1}H NMR (400.134 MHz) and ^{13}C NMR (100.6 MHz) spectra were measured in $CDCl_3$ using a Bruker AM 400 spectrometer with TMS as an internal standard. Coupling constants are expressed in Hz. Mass spectra were recorded on a Finnigan MAT 8430 instrument at 70 eV. Elemental analyses were carried out in the Microanalysis Centre of the Institut für Anorganische Chemie, Technische Universität Braunschweig. For preparative thin layer chromatography (PLC), glass plates (20 × 48 cm) were covered with a slurry of silica gel Merck PF_{254} and air-dried using the solvents listed for development. Zones were detected by quenching of indicator fluorescence upon exposure to 254 nm light; elution of the different bands with toluene afforded the pure products.

Starting materials

N-Imidoylthioureas **2a–e** were prepared according to ref. 16.

General procedure

Into a 250 cm^3 two-necked round bottom flask containing a solution of **2a–e** (2 mmol) in absolute ethanol (100 cm^3), a solution of **1** (0.412g. 2 mmol) in absolute ethanol (20 cm^3) was added dropwise with stirring. The mixture was stirred at room temperature for 1 h, then at reflux for 10–16 h (the reaction was monitored by TLC analyses). The solvent was evaporated under vacuum and the formed solid products were purified by dissolving them in dry acetone (30 cm^3) and then subjected to preparative plate chromatography (silica gel), toluene: ethyl acetate (10:1). Phenyl isothiocyanate was separated as the fastest migrating zone and was analysed by TLC analysis. The obtained products **5a–e** were recrystallised from the stated solvents.

3-(4-Methoxyphenyl)-2,5,6-triphenylpyrimidin-4(3H)-one (**5a**): Compound **5a** was obtained as yellow crystals (0.37 g, 80%), m.p. 220°C (ethanol). ^{1}H NMR (DMSO-d$_6$): δ = 7.88 (dd, 2 H, J = 8.00, 1.2 Hz, Ar–H), 7.40–7.20 (m, 9 H, Ph–H), 7.00–6.82 (m, 6 H, Ph–H), 6.75 (dd, 2 H, J = 8.0, 1.2 Hz, Ar–H), 3.95 (s, 3 H, OCH_3). ^{13}C NMR: δ = 168.8 (*C*-4), 162.1 (*C*-2), 150.9 (OCH_3–Ph–*C*), 145.9 (*C*-6), 132.0 (CH_3O–Ph–N–*C*), 131.4, 130.6, 130.2 (Ph–*C*), 128.5, 128.2, 127.8, 127.6 (*ortho*-2Ph–*C*H), 127.4, 127.2, 127.0, (*meta*-2Ph–*C*H), 126.6, 126.4, 126.0 (*para*-Ph–*C*H), 125.0 (*meta*-2Ph–*C*H),

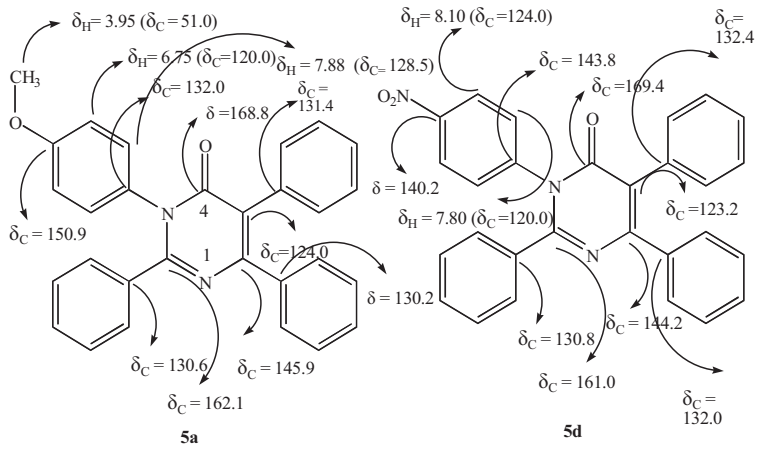

Fig. 1 Distinctive δ values of compounds **5a** and **5d**.

123.2 (*C*–5), 51.0 (OCH_3). IR (KBr): 3070-3008 (w, Ar–CH), 2960–2860 (m, aliph.-CH), 1695 (s, CO), 1612 (s, C=N), 1540 (m, C=C), 1450 (s), 918 (m) cm^{-1}. λ_{max} (CH_3CN, lg ε, nm): 360 (3.4). MS (*m/z,%*): 430 [M^+] (100), 353 (32), 338 (22), 260 (26), 150 (60), 108 (42), 77 (30). $C_{29}H_{22}N_2O_2$ (430.51): Calcd: C, 80.91; H, 5.15; N, 6.51. Found: C, 80.80; H, 5.10; N, 6.50.

3-(4-Methylphenyl)-2,5,6-triphenylpyrimidin-4(3H)-one (**5b**): Compound **5b** was obtained as yellow crystals (0.32 g, 76%), m.p. 263–265°C [lit.[20] 262–264].

3-(4-Chlorophenyl)-2,5,6-triphenylpyrimidin-4(3H)-one (**5c**): Compound **5c** was obtained as pale yellow crystals (0.30 g, 70%), m.p. 192°C (ethanol). ^{1}H NMR: δ = 7.56–7.50 (m, 2 H, Ph–H), 7.40–7.12 (m, 7 H, H-16,20), 7.00–6.80 (m, 6 H, Ph–H), 6.75–6.64 (m, 4 H, Ph–H). ^{13}C NMR: δ = 168.0 (*C*-4), 162.0 (*C*-2), 145.2 (*C*-6), 134.0 (Cl–Ph–*C*), 130.4, 129.6, 128.8, 128.4 (Ph-*C*), 128.0, 127.8, 127.6, 127.2 (*ortho*-2Ph–*C*H), 127.0, 126.8, 126.4 (*meta*-2Ph–*C*H), 126.6, 126.4, 126.0 (*para*-Ph–*C*H), 123.0 (*C*–5), 121.0 (Cl-2Ph–*C*H). IR (KBr): 3080–2990 (m, Ar–CH), 1690 (s, CO), 1612 (s, C=N), 1580 (s, C=C), 916 (m) cm^{-1}. λ_{max} (CH_3CN, lg ε, nm): 348 (3.4). MS (*m/z,%*): 435 [M + 2] (30), 434 [M^+] (100), 356 (24), 323 (24), 321 (28), 246 (24), 244 (28), 192 (32), 190 (54), 114 (24), 112 (36), 77 (50). $C_{28}H_{19}ClN_2O$ (434.93): Calcd; C, 77.33; H, 4.40; Cl, 8.15; N, 6.44. Found; C, 77.46; H, 4.36; Cl, 8.10; N, 6.39.

3-(4-Nitrophenyl)-2,5,6-triphenylpyrimidin-4(3H)-one (**5d**): Compound **5d** was obtained as pale orange crystals (0.21 g, 60%), m.p. 250°C (methanol). ^{1}H NMR: δ = 8.10 (dd, 2 H, *J* = 8.0, 1.2 Hz, NO_2Ph), 7.80 (dd, 2 H, *J* = 8.0, 1.2 Hz, NO_2Ph), 7.60–7.20 (m, 8 H, Ph–H), 7.00–6.80 (m, 7 H, Ph–H). ^{13}C NMR: δ = 169.4 (*C*-4), 161.0 (*C*-2), 144.2 (*C*-6), 143.8 (N–*C*–PhNO_2), 140.2 (NO_2–Ph–*C*), 132.4, 132.0, 130.8 (Ph–*C*), 129.6, 129.4, 129.0 (*ortho*-2Ph–*C*H), 128.6, 128.4, 128.0 (*meta*-2Ph–*C*H), 127.4, 127.0, 126.0 (*para*-Ph–*C*H), 124.0 (NO_2–2Ph*C*H), 123.2 (*C*–5), 120.0 (NO_2–2Ph*C*H). IR (KBr): 3070–2990 (w, Ar–CH), 1700 (CO), 1610 (s, C=N), 1496 (s, C=C), 920 (s) cm^{-1}. λ_{max} (CH_3CN, lg ε, nm): 340 (3.3). MS (*m/z,%*): 445 [M^+] (100), 368 (32), 322 (30), 290 (24), 262 (16), 246 (30), 240 (34), 192 (30), 169 (24), 122 (28), 77 (40). $C_{28}H_{19}N_3O_3$ (445.48) Calcd; C, 75.49; H, 4.30; N, 9.43. Found; C, 75.30; H, 4.22; N, 9.40.

2,3,5,6-Tetraphenylpyrimidin-4(3H)-one (**5e**): Compound **5e** was obtained as yellow crystals (0.25 g, 74%), m.p. 296°C [lit.[22,25] 295–296°C].

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