Reaction of amidrazones with 2,3-diphenylcyclopropenone: Synthesis of 3-(aryl)-2,5,6-triphenylpyrimidin-4(3*H*)-ones

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Amidrazones react with 2,3-diphenylcyclopropenone to give 3-aryl-2,5,6-triphenylpyrimidin-4(3*H*)-one derivatives in good yields. The synthesised compounds were characterised by spectroscopic tools and their structures confirmed by X-ray crystallography. A rational mechanism of formation of the products is presented.

Keywords: amidrazones, cyclopropenone, pyrimidine-4(3*H*)-one, ammonia extrusion, X-ray structure analysis

Cyclopropenones are reactive towards dipolar reagents and compounds having a reactive π-system.[1–3] They undergo several interesting cycloaddition reactions, and they may be useful starting materials for a variety of compounds.[4,5] There is systematic interest in the use of cyclopropenone chemistry to construct a wide variety of heterocycles.[6,7] 2,3-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 [2π + 3π] cycloaddition reactions.[8–13] In contrast, the reaction of **1** with guanidine and its alkyl and/or aryl derivatives gives the corresponding 5,6-dihydropyrimidin-4(1*H*)-ones *via* a formal [3π + 3π] cycloaddition reaction.[14] 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.[15,16] It is expected that the use of cyclopropenones as C-3 synthetic blocks will find a broader applicability in the field of synthetic chemistry in the future. 2,3-Diphenylcyclopropenone (**1**) can be represented by the resonance structures **1a**–**d**,[1–3] which contain a three-membered ring of sp^2 carbons coupled to the electron-donor substituents on the phenyls, which seem to stabilise these structures (Fig. 1).

We have examined the reactivity of amidrazones towards π-acceptors. For example, various benzo- and naphtho-1,2,4-triazin-6(4*H*)-ones (R = H, Me, MeO, Cl) are formed in one step *via* the reactions of amidrazones with benzo- and naphtho-1,4-quinones. In contrast, the reactions of amidrazones with 2,3,5,6-tetrachloro-1,4-benzoquinone or 2,3-dichloro-1,4-naphthoquinone gave indazoles.[17] Recently, we reacted amidrazones with 2-cyano-3,3-bis(methylthio)acrylate to give mercapto pyrazole derivatives.[18]

We have also investigated the chemistry of **1** in heterocyclic synthesis, such as pyridazinethiones, 1,2,4-triazolo[4,3-*b*] pyridazinethiones[19] and [2.2]paracyclophane-based pyrroles.[20] Compound **1** also reacted with ylidene-*N*-phenylhydrazine-carbothioamides to give the pyrrolo[2,1-*b*]-1,3,4-oxadiazoles.[21] On the other hand, **1** reacted with *N*-imidoylthioureas **2a**–**e** to form the pyrimidin-4(3*H*)-ones **3a**–**e**.[22] The reaction mechanism can be described as being due to stepwise addition accompanied by elimination of phenyl isothiocyanate (Scheme 1).[22]

Depending upon the encouraging aforementioned results, compound **1** can react with different nucleophiles to produce various heterocycles. We herein investigate the reactivity of amidrazones **4a**–**f** towards **1**.

Results and discussion

Thus, on reacting cyclopropenone **1** with amidrazones **4a**–**f**[23] in ethanol and catalysed by a few drops of triethylamine, the reaction proceeded, surprisingly, to give 3-aryl-5,6-

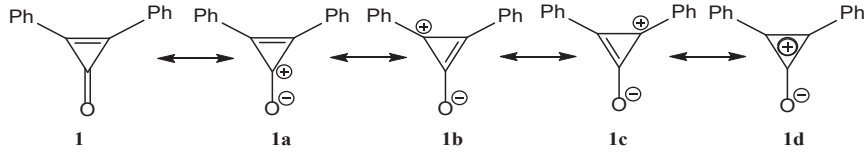
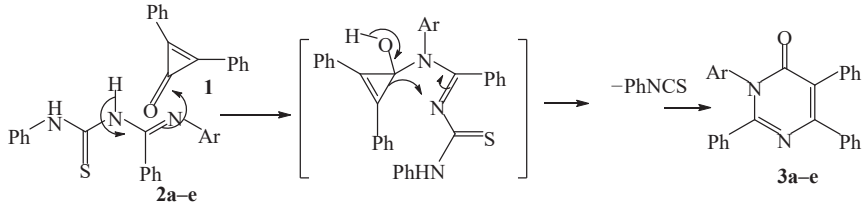


Fig. 1 Resonance structures of 2,3-diphenylcyclopropenone (**1**).



Scheme 1 Pyrimidin-4(3*H*)-ones **3a**–**e** from reaction of *N*-imidoylthioureas **2a**–**e** with **1**.

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diphenylpyrimidin-4(3*H*)-ones **5a–f** in 67–87% yields (Scheme 1). We chose compounds **4a–f** having aryl groups with electron-donating and withdrawing substituents on the benzene ring in order to examine their reactivity. The structure proof of **5a–f** was based on the mass, ^{1}H NMR, ^{13}C NMR and IR spectra as well as X-ray structure analysis, together with elemental analyses. For example, the reaction of compound **4a** with **1** for 7 h yielded yellow crystals of **5a** in 83% yield (Scheme 2). The NMR spectroscopic data of compounds **5a** and other derivatives **5b**, **5d** and **5e** were found to be similar to those reported in the literature[22]. The structure was unambiguously proved during X-ray structure analysis of compound **5e** (Fig. 2). However, the structures of the newly prepared pyrimidin-4-one derivatives, as found in **5c** and **5f**, were proved by NMR, mass and IR spectra and elemental analyses (see Experimental section). In the case of **5c**, the mass spectrum and elemental analysis proved the molecular formula to be $C_{30}H_{24}N_2O$. The ^{1}H NMR spectrum of **5c** showed a singlet at $\delta_H = 2.06$. The di-*ortho*-substituted phenyl group showed a broad doublet $\delta_H = 6.92$ ($J = 7.5$; 2H) and a triplet at $\delta_H = 6.81$ ($J = 7.3$ Hz, 1H) (see Experimental section). Characteristic resonances representing the carbonyl carbon (C-4) and C-6 resonated in the ^{13}C NMR spectrum at $\delta_C = 166.6$ and 155.3, respectively. Besides, the azomethine carbon of N=C–N which appeared in the ^{13}C NMR spectrum at $\delta_C = 156.2$, whereas the carbon of N–C–Ar appeared at $\delta_C = 144.2$. In the case of **5f**, the ^{13}C NMR spectrum revealed C-4, N=C–N, C-6 and N–C–Ar at $\delta_C = 161.6$, 157.31, 157.26 and 137.9, respectively. The N-3 resonates in ^{15}N NMR at $\delta_N = 187.3$ (N-3). Interestingly, the product formation excluded the formal [2 + 3] cycloaddition pathways proposed by Eicher.[8–13] The reaction mechanism can be simply described as due to the hydrazine addition to C-2 of **1** leading to intermediate **6**. Thereafter amidine-like reaction of N-3 to the carbonyl might occur to form salt **7** (Scheme 3). Nucleophilic addition *via* ring opening to the positively charged nitrogen followed by proton transfer would give **8**. Elimination of ammonia from **8** would ultimately give **5** (Scheme 3). In further support, 3-substituted 5,6-diphenylpyrimidin-4-ones were obtained from diphenylcyclopropenone and *N*-substituted amide oximes. Reaction proceeded *via* elimination of water from the oxime moiety.[24]

Interestingly, in this paper we report on the first article dealing with the removal of ammonia from amidrazone reactions. Clearly indicative is the first X-ray structure analysis of substituted 2,5,6-triphenylpyrimidin-4(3*H*)-ones. As amidrazones can be prepared with various aliphatic and aromatic substituents from easily available thioamides[23], accordingly, various pyrimidine-4-ones of **5** can be prepared. Moreover, reaction between **4a–f** and **1** takes place smoothly and the reaction can be considered as one-pot.

Conclusions

In this paper, we report another new reactivity of amidrazones *via* extrusion of ammonia from N-1. Hence, further investigation of amidrazones will be valuable. Although 2,5,6-triphenylpyrimidin-4(3*H*)-ones are known structures, the above procedure is shown to be a more effective, easier and high-yield route to these products.

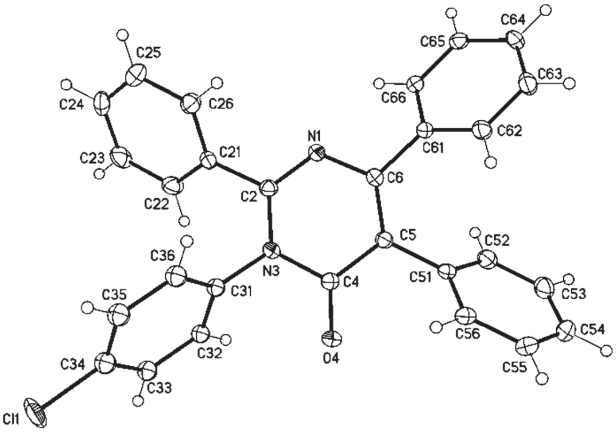
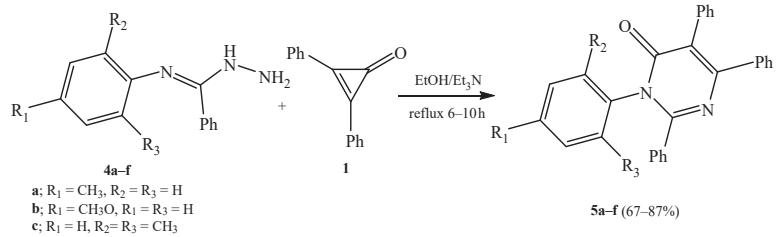
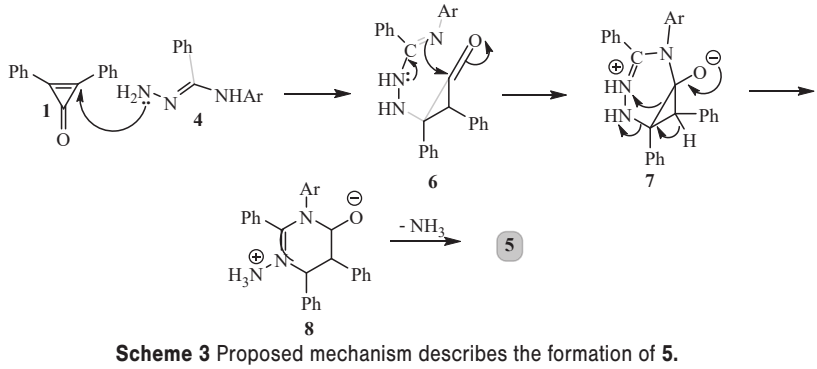


Fig. 2 Molecular structure of 3-(4-chlorophenyl)-2,5,6-triphenylpyrimidin-4(3*H*)-one (**5e**) (the minor disordered part is omitted for clarity; displacement parameters are drawn at the 50% probability level).



5a (83%); **5b** (87%); **5c** (86%); **5d** (60%); **5e** (72%); **5f** (67%)

Scheme 2 Synthesis of pyrimidine-4-ones **5a–f** from reaction of amidrazones **4a–f** with 2,3-diphenylcyclopropenone (**1**).



Scheme 3 Proposed mechanism describes the formation of **5.**

Experimental

A Gallenkamp melting point apparatus was used to determine melting points (Weiss-Gallenkamp, Loughborough, UK); the results are uncorrected. The IR spectra (recorded in KBr) were recorded with an Alpha Bruker FTIR and a Shimadzu 408 instrument. The NMR spectra were measured using a Bruker AV-400 (Florida Institute of Technology, USA). Chemical shifts are expressed as δ (ppm) with tetramethylsilane (TMS) as internal reference; s = singlet, t = triplet, q = quartet, m = multiplet, br. = broad; the ^{13}C NMR signals were assigned on the basis of DEPT 135/90 spectra. Chemical shifts are expressed as δ in parts per million (ppm). The mass spectra (70 eV, electron impact mode) were recorded with a Finnigan MAT 8430 instrument. The elemental analyses for C, H, N and S were carried out at the Microanalytical Centre, Cairo University, Egypt with an Elmyer 306 Analyzer. Preparative layer chromatography was performed with air-dried 1.0 mm layers of slurry-applied silica gel (Pf254, Merck, Germany) on glass plates 48 × 20 cm using the solvents indicated.

General procedure

Into a 250 mL two-necked round bottom flask containing a solution of **4a–f** (2 mmol) in absolute ethanol (50 mL), a solution of **1** (0.412 g, 2 mmol) in absolute ethanol (20 mL) was added dropwise with stirring. The mixture was stirred at room temperature for 1 h, then at reflux for 6–10 h (the reaction was monitored by TLC analyses). The solvent was evaporated under vacuum and the solid products formed were purified by dissolving them in dry acetone (30 mL) and then subjecting them to preparative plate chromatography (silica gel) with toluene–ethyl acetate (10:1). The products **5a–f** obtained were recrystallised from the stated solvents.

3-(4'-Methylphenyl)-2,5,6-triphenylpyrimidin-4(3H)-one (**5a**): Compound **5a** was obtained as yellow crystals (0.34 g, 83%), m.p. 263–265 °C (EtOH) [lit.[22] 262–264 °C].

3-(4'-Methoxyphenyl)-2,5,6-triphenylpyrimidin-4(3H)-one (**5b**): Compound **5b** was obtained as yellow crystals (0.37 g, 87%), m.p. 220 °C (CH_3CN) [lit.[22] 220–222 °C].

3-(2',6'-Dimethylphenyl)-2,5,6-triphenylpyrimidin-4(3H)-one (**5c**): Compound **5c** was obtained as yellow crystals (0.37 g, 86%), m.p. 212–214 °C (EtOH); ^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 7.80–7.74 (m, 2H, Ph–H), 7.65–7.53 (m, 4H, Ph–H), 7.43–7.24 (m, 5H, Ph–H), 7.18–7.14–7.11 (m, 4H, Ph–H), 6.92–6.90 (br., 2H, *J* = 7.5 Hz, Ar–H-*o*), 6.81–6.79 (t, 1H, *J* = 7.3 Hz; Ar–H-*p*), 2.06 (s, 6H, CH_3); ^{13}C NMR: δ_C = 166.6 (C-4), 156.2 (N=C–N), 155.3 (C-6), 144.2 (N–C–Ar), 134.4 (Ar–2C–CH_3), 133.8, 133.2, 132.0 (Ar–C), 128.9, 128.6, 128.4, 128.2 (*ortho*-2Ar–CH), 127.6, 127.4, 127.0 (*meta*-Ar–2CH), 126.8, 126.6, 126.0 (*para*-Ph–CH), 112.2 (C-5), 22.0 ($2CH_3$); IR (KBr) ν_{max} cm^{-1}: 3080–3012 (w, Ar–CH), 2965–2840 (m, aliph.–CH), 1695 (s, C=O), 1610 (s, C=N), 1540 (m, C=C); MS (*m/z*, %): 428 [M$^+$] (100), 352 (30), 337 (18), 322 (28), 316 (24), 240 (18), 150 (38), 108 (40), 77 (34). Anal. calcd for $C_{30}H_{24}N_2O$ (428.54): C, 84.08; H, 5.65; N, 6.54; found: C, 83.85; H, 5.50; N, 6.70%.

3-(4'-Nitrophenyl)-2,5,6-triphenylpyrimidin-4(3H)-one (**5d**): Compound **5d** was obtained as pale orange crystals (0.27 g, 60%), m.p. 250 °C (EtOH). [lit.[22] 250 °C].

3-(4'-Chlorophenyl)-2,5,6-triphenylpyrimidin-4(3H)-one (**5e**): Compound **5e** was obtained as pale yellow crystals (0.31 g, 72%), m.p. 192 °C (MeOH) [lit.[22] 192 °C].

3-(4'-Bromophenyl)-2,5,6-triphenylpyrimidin-4(3H)-one (**5f**): Compound **5f** was obtained as yellow crystals (0.32 g, 67%), m.p. 195–197 °C ($CHCl_3$/cyclohexane); ^{1}H NMR (400 MHz, DMSO-d_6): 7.56 (d, 2H, *J* = 8.5 Hz), 7.45 (d, 2H, *J* = 6.8 Hz), 7.38 (m, 4H), 7.29 (m, 8H), 7.25 (m, 4H); ^{13}C NMR: δ_C = 161.6 (C-4), 157.31 (N=C–N), 157.26 (C-6), 137.9 (N–C–N), 137.0, 134.9, 134.1, 131.6 (Ar–C), 131.4), 130.8, 129.6, 129.5, 129.1, 128.8, 127.9, 127.8 (2CH), 127.4, 122.4, 121.5 (CH); IR (KBr) ν_{max} cm^{-1}: 3090–3010 (w, Ar–CH), 1695 (s, C=O), 1612 (s, C=N), 1560 (m, C=C); ^{15}N NMR: δ_N = 187.3 (N-3); MS (*m/z*, %): 480 (30), 479 (156), 478 (28), 400 (34), 322 (20), 246 (18), 170 (24), 92 (28), 77 (40). Anal. calcd for $C_{28}H_{19}BrN_2O$ (479.38): C, 70.16; H, 4.00; N, 5.84; found: C, 70.00; H, 4.10; N, 5.75%.

Single crystal X-ray structure determinations of **5e**

The single crystal X-ray diffraction study was carried out on a Bruker D8 Venture diffractometer with Photon100 detector at 123 K using Mo Kα radiation (λ = 0.71073 Å). Direct methods (SHELXS-97)[25] were used for the structure solution, and refinement was carried out using SHELXL-2014)[26] (full-matrix least-squares on F^2). Hydrogen atoms were localised using a difference Fourier synthesis map and refined using a riding model. A semi-empirical absorption correction was applied. The *p*-chlorophenyl-group is disordered. Refinement with the listed atoms show residual electron density due to a heavily disordered methanol around a centre of symmetry which could not be refined with split atoms. Therefore the 'SQUEEZE' option of the program package PLATON[27] was used to create an hkl file taking into account the residual electron density in the void areas. Therefore, the atoms list and unit card do not agree (see cif-file for more details). Compound **3e**: $C_{28}H_{19}ClN_2O \cdot 0.5\ CH_3OH$, Mr = 450.92 g mol^{-1}, yellow blocks, size 0.32 × 0.14 × 0.12 mm, triclinic, P-1 (No. 2), a = 9.6540(6) Å, b = 10.5370(7) Å, c = 11.6531(8) Å, α = 79.706(2)°, β = 78.519(2)°, γ = 77.126(2)°, V = 1121.23(13) Å^3, Z = 2, D_{calcd} = 1.336 Mg m^{-3}, *F* (000) = 470, μ = 0.197 mm^{-1}, T = 123 K, 42,804 measured reflections ($2\theta_{max}$ = 55°), 5168 independent [R_{int} = 0.028], 263 parameters, 36 restraints, R_1 [for 4540 I > 2σ (I)] = 0.047, wR_2 (for all data) = 0.122, *S* = 1.03, largest diff. peak and hole = 0.595 e Å^{-3}/–0.666 e Å^{-3}. CCDC 1476780 (**5e**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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