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One-pot synthesis of 3-arylaminomaleimides from terminal alkynes and isocyanates

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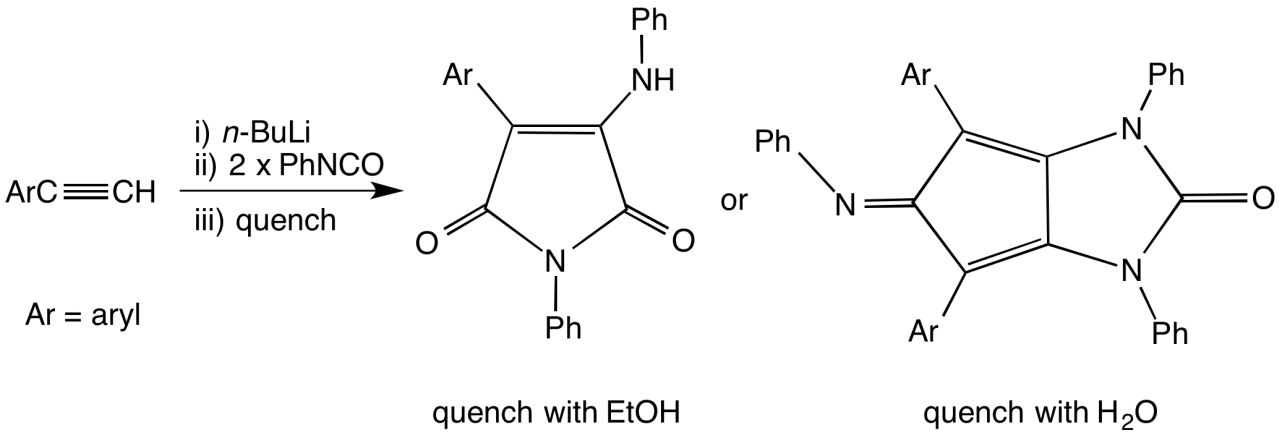
Graphical Abstract



Abstract

The reaction of aryl acetylide anions with phenyl isocyanate and subsequent addition of a protonating agent such as ethanol affords good yields of 3-aminomaleimides, formed by the cyclization of one molecule of alkyne with two isocyanates. When the reaction is quenched with water instead, cyclopentadienone imines are formed as the major products.

Keywords

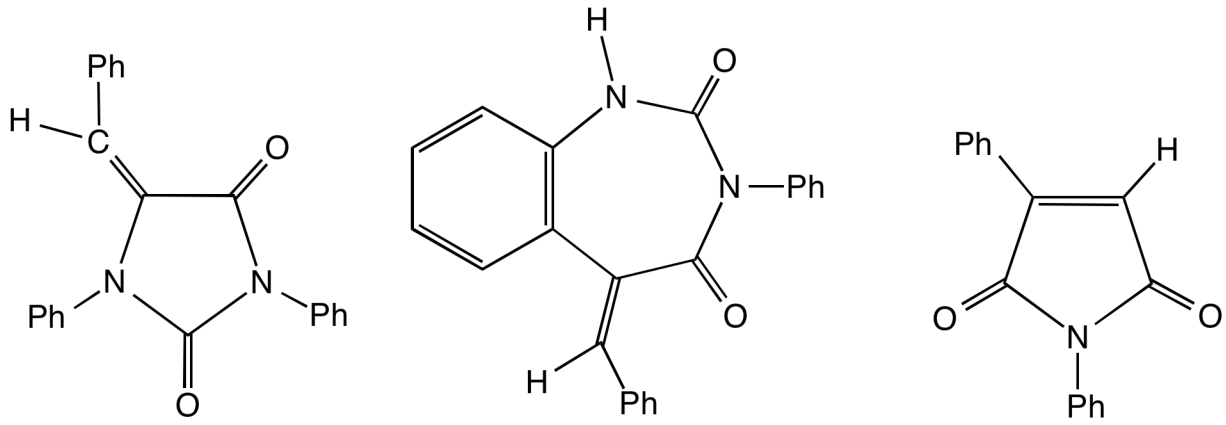
Acetylide; Alkyne; Isocyanate; Hydantoin; Heterocycle; Maleimide

As part of a recent research effort targeted towards the synthesis of heterocycles from acetylide anions and heterocumulenes, we have reported the efficient production of 1,2-dithiole-3-thiones under very mild conditions from deprotonated terminal alkynes, CS_2 and elemental sulfur. Replacement of carbon disulfide by isothiocyanates gave access to the related 3-imino-1,2-dithioles.[1] More recently we have shown that the reaction of aryl acetylides with phenyl isothiocyanate, followed by the addition of ethanol, leads to the formation of an unusual thiazolidine heterocycle which is a dimer of the acetylenic thioamide PhC≡CC(=S)NHPh.[2]

We have now extended these investigations to isocyanates and herein report that cyclization of aryl acetylides with phenyl isocyanate proceeds with the formation of 3-arylaminomaleimides. Such compounds are of interest both as inhibitors of glycogen synthase kinase 2 (GSK-2)[3] and also as fluorophores and species that display the phenomenon of aggregate-induced emission.[4]

The reaction of phenylacetylene and its organometallic derivatives with phenyl isocyanate is one with a long and surprisingly complicated history. Perhaps the seminal works in this area were the initial investigations of Tyabji, later followed up by Bird, who studied the reaction of sodium phenylacetylide with PhNCO in diethyl ether, hydrolysing the mixture with ethanol, water and HCl.[5,6] Two products were isolated and identified spectroscopically as the 5-benzylidene hydantoin **1** and the benzylidene benzodiazepinedione **2** (Fig. 1). Subsequently, the same hydantoin was prepared by heating PhC≡CH with PhNCO in the presence of either $[Fe(CO)_5]$[7] or $[Mn(CO)_5Br]$[8], by the reaction of PhC≡CBr with PhNCO and $[Fe(CO)_5]$,[9] and by treating PhNCO with phenylalkynyl derivatives of lead.[10] More recently Mathur and co-workers have established that heating PhC≡CH with PhNCO and $[Fe(CO)_5]$ under nitrogen produced the hydantoin **1**, whereas in

a CO atmosphere the maleimide derivative **3** was formed by cyclisation of one alkyne molecule with one PhNCO and one CO derived from the metal carbonyl.[11] Earlier papers claim that the acetylenic Grignard PhC≡CMgBr reacts with PhNCO to give only the anilide PhC≡CC(=O)NHPh,[10, 12] and lithiation of ethyl propiolate and reaction with PhNCO at low temperature was also shown to proceed only as far as the amide $EtO_2CC{\equiv}CCONHPh$.[13] More recently the reaction of PhC≡CH with dibutyl magnesium and PhNCO was shown to give a bis(imidazolidine-2,4-dione).[14]



1 **2** **3**

Figure 1. Previously isolated products from the reaction of PhC≡CH with PhNCO.

The deprotonation of phenylacetylene with *n*-BuLi and addition of PhNCO (2 equiv.) at –78 °C, followed by warming to room temperature, caused a rapid colour change to intense orange-red. After quenching with ethanol or several other protonating agents (e.g. $[NH_2Et_2][Br]$ or acetic acid), chromatographic work-up produced a bright orange compound which, according to its mass spectrum (*m*/*z* 340), contained one phenylacetylene unit and two isocyanates. However its ^1H NMR spectrum did not correspond to that of hydantoin **1**, and moreover its IR spectrum contained an unmistakable N–H peak.[15, 16] Single crystal X-ray structural determination (Fig. 2) established its structure as the aminomaleimide derivative **4a** (Scheme 1).

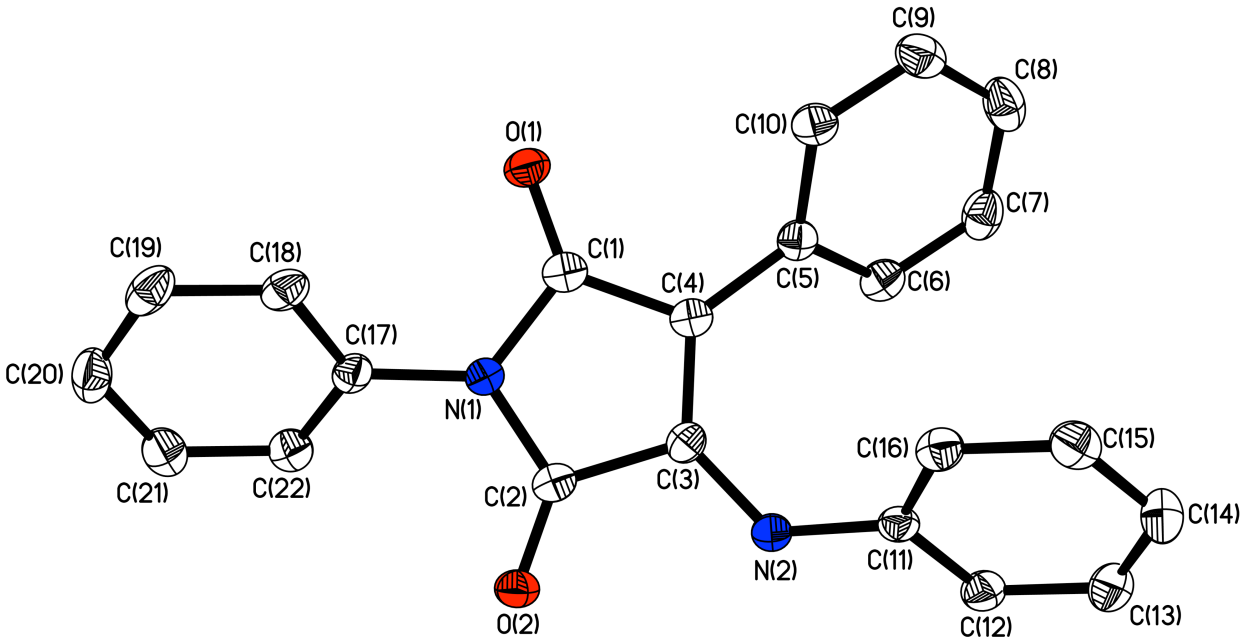
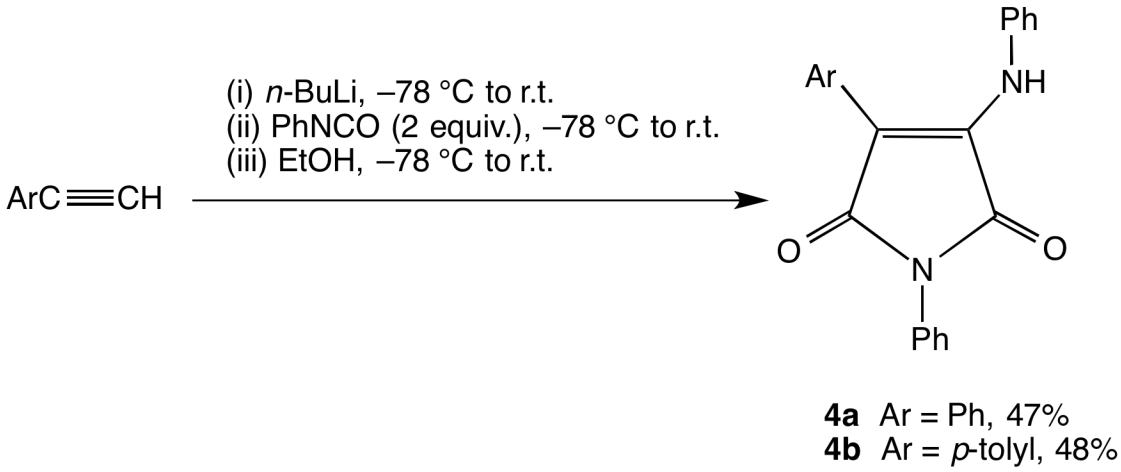


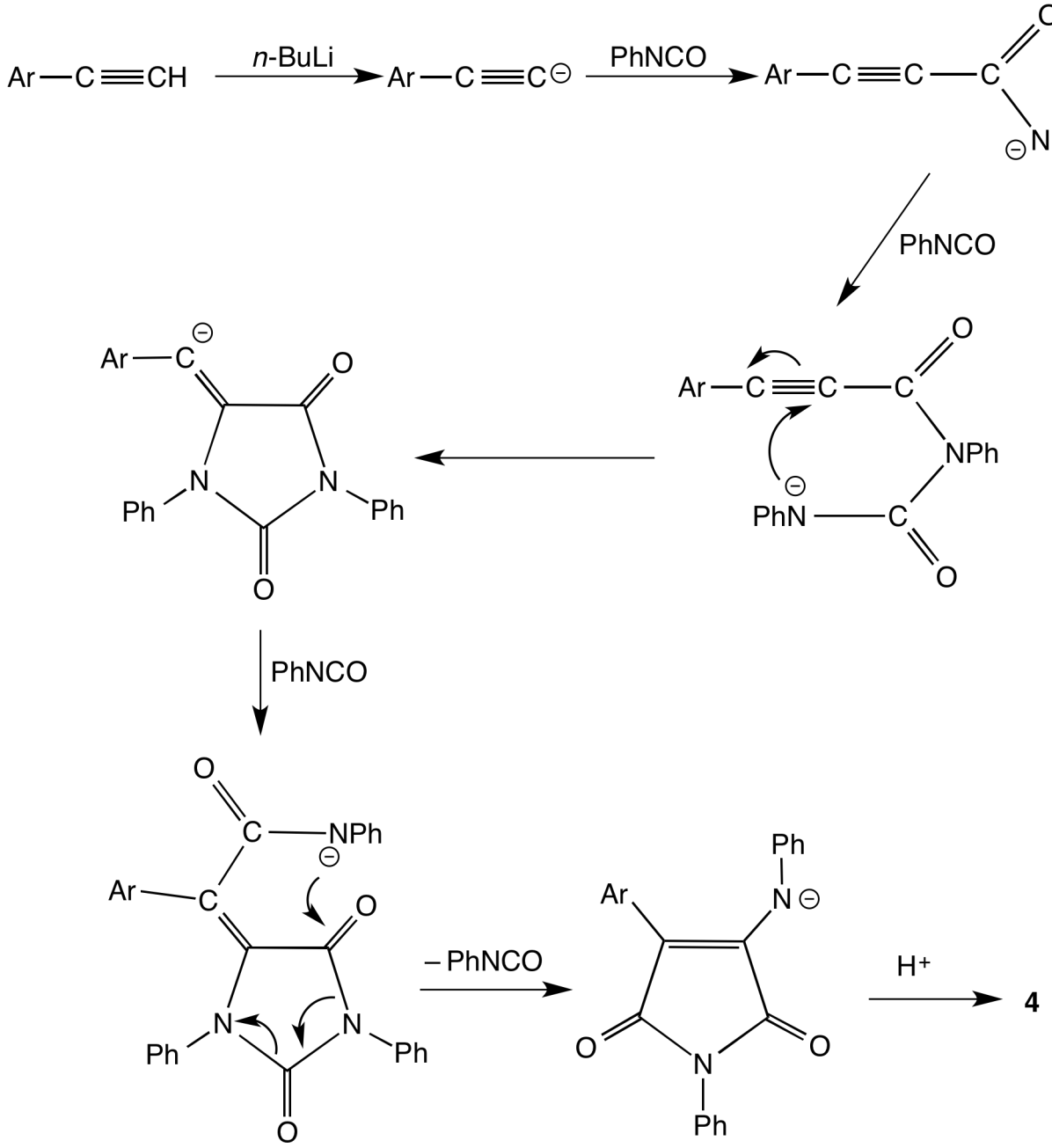
Figure 2. Molecular structure of **4a** in the crystal.



Scheme 1. Formation of the aminomaleimides.

The IR spectrum, melting point and UV-visible spectrum of **4a** did however match those reported for Bird's minor product, originally identified as **2**. We therefore attempted to repeat Bird's reaction, using sodium phenylacetylide in diethyl ether. In our hands, this gave a mixture of hydantoin **1** and maleimide **4a** that was to an extent separable by column chromatography. We therefore suspect that the true identity of Bird's minor product is **4a**.

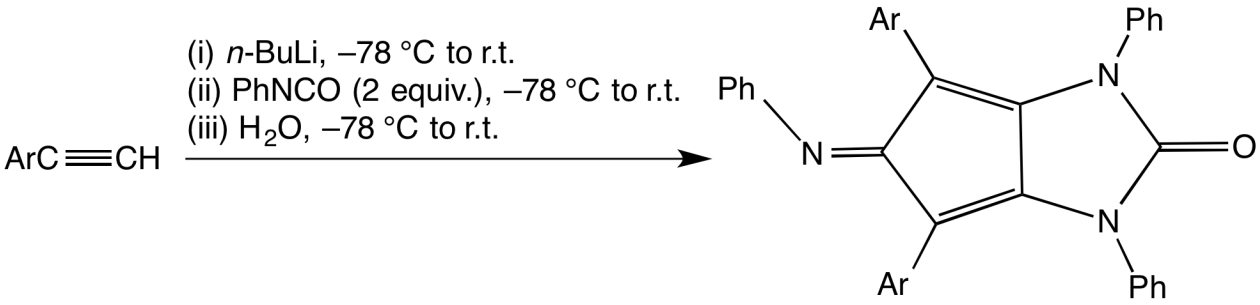
Under our conditions the formation of hydantoin **1** is completely suppressed. If the temperature of the reaction is maintained at –78°C after the addition of PhNCO and the reaction is quenched without warming, **4a** is still isolated but in lower yield and as a mixture with PhC≡CC(=O)NHPh,[17] and a small amount of hydantoin **1** is also formed. One possible mechanism for the formation of **4** in the presence of excess PhNCO is shown below. Attempts to cause the rearrangement of hydantoin **1** to **4a** by stirring it in base (LiOEt), with or without additional isocyanate, were however unsuccessful.



Scheme 2. Possible mechanism for the production of the aminomaleimides.

In contrast to the aryl acetylenes, other terminal alkynes were more reluctant to react in an analogous manner. Thus, ferrocenyl acetylene, while producing a compound of type **4** in low yield, also gave a second compound which was identified as the acetylenic amide FcC≡CC(=O)NHPh. When ^{t}BuC≡CH was lithiated and allowed to react with PhNCO, a white precipitate was deposited; upon work-up the amide ^{t}BuC≡CC(=O)NHPh was isolated in virtually quantitative yield.[18]

Comments in Bird's paper[6] to the effect that the reaction only worked in conditions of high humidity also led us to investigate the effect of quenching the reaction with water instead of ethanol. Remarkably in this case the yield of **4** is drastically reduced and a new product **5** is isolated as a red solid (Scheme 3).[19] Compared to **4a** and **4b**, the mass spectra of **5a** and **5b** unexpectedly showed increased molecular masses with molecular ions at *m/z* 515 and 543, respectively. The latter compound was readily crystallized from CH_2Cl_2 and light petroleum as red blocks, which were identified by single crystal X-ray analysis as the cyclopentadienone imine **5b** (Fig. 2). The mechanism for the formation of **5** is currently obscure, involving two alkyne molecules, three isocyanates, and the apparent elimination of the elements of CO_2 from the latter. However the reaction provides a convenient route to these previously unknown dienes, and given the fact that such bicyclic imines are accessed only with difficulty,[20] and their similarity to the ligands used in Shvo/Knölker-type hydrogenation/dehydrogenation catalysts, we are currently exploring their coordination to iron and ruthenium carbonyl fragments.[21]



5a Ar = Ph, 26%
5b Ar = *p*-tolyl, 17%

Scheme 3. Formation of cyclopentadienone imines.

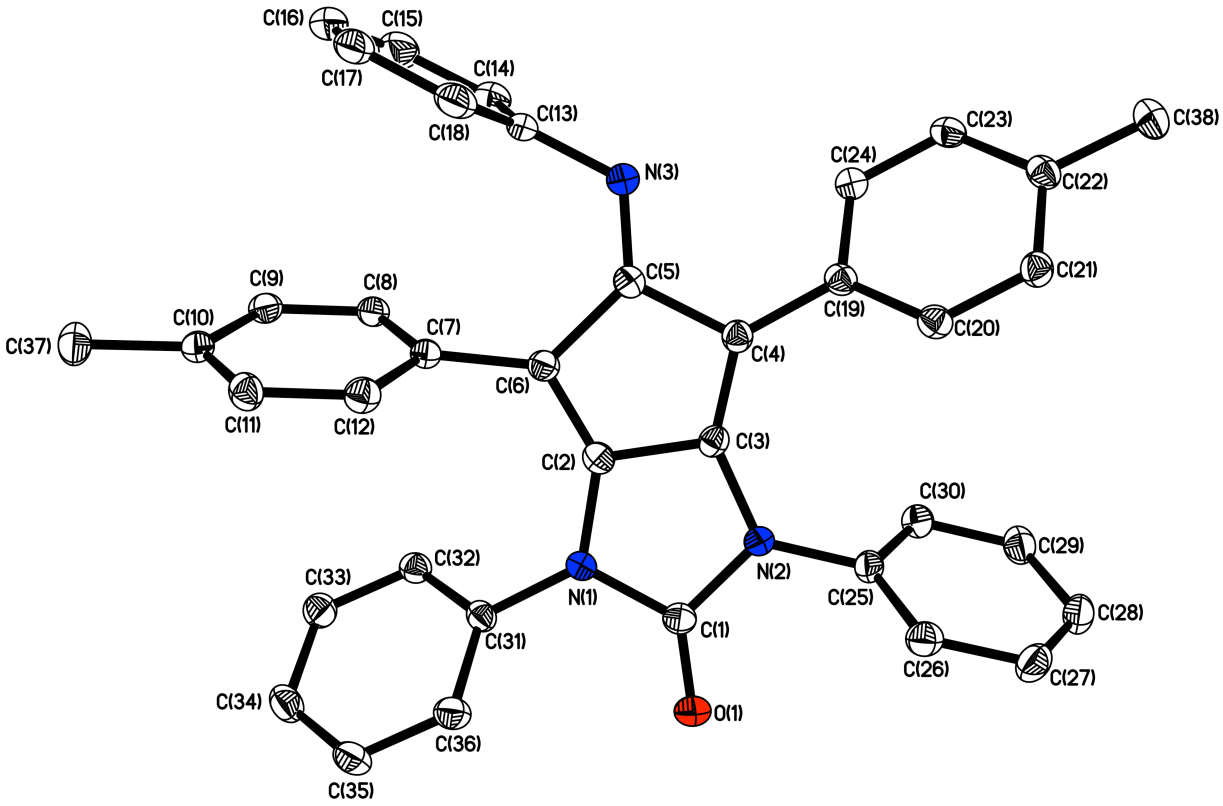


Figure 3. Molecular structure of **5b** in the crystal.

In conclusion, we have demonstrated the efficient synthesis of aminomaleimide heterocycles from terminal aryl alkynes and phenyl isocyanate, and by quenching the reaction with water instead of ethanol that the major product can be changed to a previously unknown cyclopentadienone imine. It is noticeable that in contrast to our earlier work with CS_2 and PhNCS, the more reactive isocyanate only gives rise to products containing multiple heterocumulene molecules.

Acknowledgements

We thank the University of Sheffield for support, and Prof. Joe Harrity for useful discussions. This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

Supplementary data

Crystallographic data for the structure determinations of **4a** and **5b** have been deposited with the Cambridge Crystallographic Data Centre, reference numbers CCDC 1522806 and 1522805 respectively. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Supplementary data associated with this article can be found, in the online version, at...

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15. Typical experimental procedure for the synthesis of1,4-diphenyl-3-phenylaminomaleimide (**4a**).

A solution of phenylacetylene (0.58 mL, 5.28 mmol) in THF (20 mL) was cooled to –78 °C and treated with *n*-BuLi (3.3 mL of a 1.6 M solution in hexanes, 5.28 mmol), then warmed to room temperature and stirred for 30 min. After again cooling to –78 °C, PhNCO (1.15 mL, 10.59 mmol) was added; on warming to room temperature and stirring for 1 h, the solution gradually turned an intense orange-red colour. The solution was cooled to –78 °C for a third time and after addition of EtOH (3 mL), was allowed to warm to room temperature and stirred overnight. The solvent was removed *in vacuo*, the residue absorbed on a small amount of silica and introduced to the top of a silica column made up in light petroleum. Elution with light petroleum–CH_2Cl_2: (2:3, then 1:4) produced a large bright orange band of compound **4a** (840 mg, 47%). M.p. 201-203 °C. IR (CH_2Cl_2): 1769m, 1710vs, 1652s, 1597m cm^{-1}. IR (KBr): 3305s (NH). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (d, *J* = 4.3 Hz, 5 H), 7.40 (m, 1 H), 7.22-7.00 (m, 8 H), 6.72 (d, *J* = 7.5 Hz, 2 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 170.8, 167.5 (both CO), 136.2, 136.2, 131.9, 129.2 (3 C_{ipso} + CNHPh), 129.8, 129.1, 128.3, 127.5, 127.3, 125.9, 124.7, 121.7 (m, Ph), 102.5 (CPh). MS (EI): *m/z* 340 (M^+), 220, 193. UV-vis (EtOH, λ_{max} in nm, ε in $M^{-1}cm^{-1}$): 251 (ε 28450), 294sh (ε 7600), 408 (ε 6310). Analysis Found: C, 77.39; H, 4.74; N, 8.19. Calcd. for $C_{22}H_{16}N_2O_2$: C, 77.65; H, 4.71; N, 8.23%.

16. Characterisation data for **1** can be found in the Supplementary Information of reference 8. IR (CH_2Cl_2): 1772ms, 1726vs, 1657m, 1597w cm^{-1}. Notably the ^{1}H NMR spectrum of **1** in $CDCl_3$ contains a doublet at δ 6.86 instead of the doublet at δ 6.72 observed for **4a**.

17. The presence of PhC≡CC(=O)NHPh can be easily detected by its peak at δ 7.91 in the ^{1}H NMR spectrum.

18. IR (KBr): 2222 (C≡C), 1642 (CO). ^{1}H NMR (400 MHz, d^6-DMSO): δ 7.46 (t, 2 H, Ph), 7.15 (t, 2 H, Ph), 6.86 (t, 1 H, Ph), 1.21 (s, 9 H, ^{t}Bu). MS (EI): *m/z* 201 (M^+), 200, 186, 158. For comparison, see Kawaguchi, H.; Tatsumi K. *Organometallics* **1995**, *14*, 4294.

19. Typical experimental procedure for **5b**: A solution of 4-ethynyltoluene (0.63 mL, 4.94 mmol) in THF (20 mL) at –78 °C was treated with *n*-BuLi (3.1 mL of a 1.6 M solution in hexanes, 4.96 mmol), allowed to warm to room temperature and stirred for 30 min. After again cooling to –78 °C, PhNCO (1.08 mL, 9.94 mmol) was added; on warming to room temperature and

stirring for 1 h, the solution gradually turned an intense orange-red colour. After cooling the solution to –78 °C, water (1 mL) was added and the mixture allowed to warm to room temperature and stir overnight; it remained a red colour. Column chromatography as above gave a red band of **5b**, eluted in light petroleum–CH_2Cl_2: (2:3). The latter part of the band also contains a small amount of **4b**, which is easily removed by crystallization (diffusion of light petroleum into a CH_2Cl_2 solution). Yield 236.7 mg, 17%. M.p. 260-262 °C. IR (CH_2Cl_2): 1754 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.26-6.59 (m, 19 H, Ph + tol), 6.36, 6.32 (both br s, 2H, Ph), 2.28, 2.06 (both s, 3H, Me). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 166.6 (C=N), 155.5 (C=O), 149.4 (C_{ipso} of NPh), 136.3, 136.1, 133.8, 133.2, 130.9, 129.5, 128.6, 128.4, 127.6, 127.5, 127.4, 127.1, 126.7, 126.5, 126.2, 125.9, 125.3, 123.3, 120.6 (m, Ph + tol), 21.3, 21.0 (Me). MS: *m/z* 544 $(M+H)^+$. Analysis Found: C, 83.58; H, 5.45; N, 7.63. Calcd. for $C_{38}H_{29}N_3O$: C, 83.98; H, 5.34; N, 7.73%.

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Captions for Figures and Schemes

Figure 1 Previously isolated products from the reaction of PhC≡CH with PhNCO.

Figure 2 Molecular structure of **4a** in the crystal.

Figure 3 Molecular structure of **5b** in the crystal.

Scheme 1 Formation of the aminomaleimides.

Scheme 2 Possible mechanism for the production of the aminomaleimides.

Scheme 3 Formation of cyclopentadienone imines.