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ORIGINAL ARTICLE

Synthesis of 1-((4-methoxyphenyl)-3-alkynes)-1*H*-pyrrole-2,5-diones and functionalization to triazoles

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X-ray structure

Abstract A series of alkynyl maleimides were prepared via one-step cross-coupling reaction using bromomaleimide and acetylenes under the Sonogashira conditions, affording 1-((4-methoxyphenyl)-3-alkynes)-1*H*-pyrrole-2,5-diones in good to high yields. These products were subsequently converted in the corresponding 1,2,3-triazole using conventional click chemistry approach. The alkynyl maleimide compound (**8g**) crystallized in the triclinic space group P1 with unit cell parameters $a = 5.3692(6)$, $b = 9.2513(10)$, $c = 10.3070(11)$ Å, $\alpha = 85.349(4)$, $\beta = 86.892(4)$, $\gamma = 86.892(4)°$, $V = 507.31(10)$ Å^3, and $Z = 1$. In the crystal the molecules are stacked parallel to the *c* axis and held together through a C–H···π and a C–H···O interaction.

1. Introduction

Maleimides and their related compounds have invaluable properties, especially biologically, with high cytotoxicity and inhibitory activity toward protein kinase C and topoisomerase I (Lakatosh et al., 2003). Maleimides and their derivatives are potential building blocks in the frontiers of organic chemistry, such as medicinal chemistry, polymer chemistry, and material science.

Cyclic oxopyrrolidine compounds are building blocks and are versatile intermediates for the total synthesis of a wide variety of natural and unnatural compounds with interesting biological activities (Deore and Argade, 2014). Maleimides have countless pharmaceutical properties e.g. antibacterial, anticancer, antimicrobial, antiviral, and antigenic activities (Sanchez et al., 2006). Rebeccamycin, which has an oxopyrrolidine structure, is known topoisomerase I inhibitor, and exhibits antitumor activity against L1210 leukemia, B16 melanoma implanted in mice, and P388 leukemia and also inhibits the growth of human lung adenocarcinoma cells (A549) (Prudhomme, 2003; Bush et al., 1987; Nettleton et al., 1985) (Fig. 1). Among the maleimides, 3,4-disubstituted maleimides have also found applications in material science as components of red light-emitting diodes (LEDs) because of

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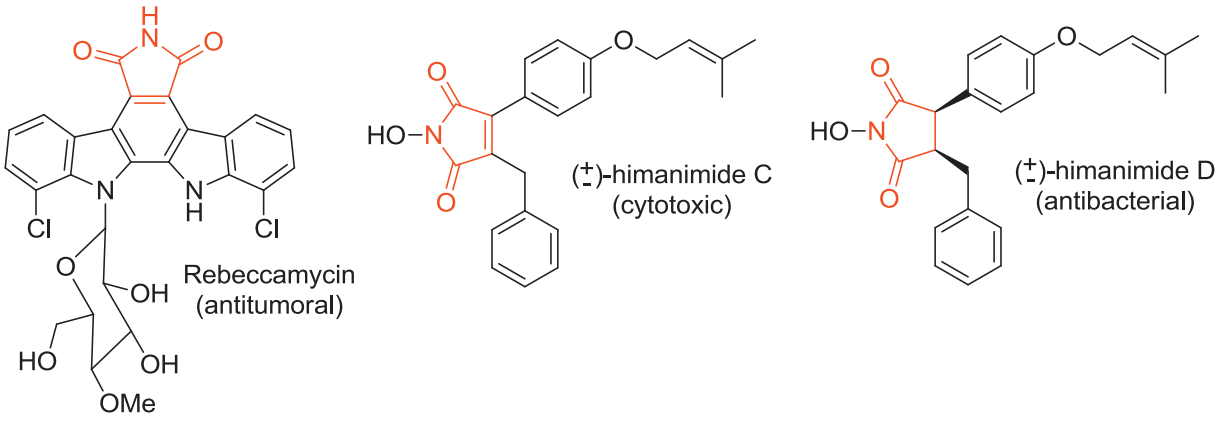


Figure 1 Maleimides with pharmaceutical properties.

their intense color (Kaletas et al., 2005a,b,c). These compounds have also been used in the development of photocatalysts immobilized on surfaces (Kaletas et al., 2005a,b,c; Souffrin et al., 2012).

Our group is also working on the development of diverse structures of oxopyrrolidines (Stefani et al., 2014a,b; Ali et al., 2015a,b) and maleimide compounds (Stefani et al., 2014a,b; Ali et al., 2015a,b; Caracelli et al., 2015). To the best of our knowledge, few practical routes are known for the synthesis of alkynyl maleimides (Pews-Davtyan et al., 2008; Brennführer et al., 2009; Bouissane et al., 2009).

Sonogashira coupling is one of the most important carbon–carbon bond forming cross-coupling reaction involving alkynes (Izgu and Hoye, 2012; Awuah and Capretta, 2011; Roshchin, 2010). Although, the Sonogashira coupling of alkynes with halomaleimides has not been described previously, only a few practical routes for palladium-catalyzed cross-coupling reactions have been reported (Deore and Argade, 2012; Banwell et al., 2010; Stewart et al., 2007; Dubernet et al., 2005). In this context, we herein report our results as the synthesis of 1-((4-methoxyphenyl)-3-triazololyl)-1*H*-pyrrole-2,5-diones and their functionalization.

2. Material and methods

All reactions were carried out under a nitrogen atmosphere; all compounds were characterized by ^{1}H NMR, ^{13}C NMR and electrospray ionization-mass spectrometry (ESI-MS). NMR spectra were recorded on a 300 MHz instrument. All ^{1}H NMR experiments are reported in δ units, parts per million (ppm), and were measured relative to the signals for tetramethylsilane (TMS) (0.00 ppm). All ^{13}C NMR spectra are reported in ppm relative to deuteron-chloroform (77.23 ppm), unless otherwise stated, and all were obtained with ^{1}H decoupling. For HRMS, previously lyophilized samples were dissolved in methanol and deposited into the 96 well plate of the SIL-20A autosampler for ESI-MS analysis in an IT-TOF mass spectrometer system (Shimadzu). The compounds were detected in positive mode. Typically, 0.1 μL sample aliquots were injected and infused into the instrument in 50% acetonitrile, containing 0.5% formic acid under a constant flow rate of 0.2 mL min^{-1}. Instrument control, data acquisition and processing were performed by the LCMS Solution suite (Shimadzu). ESI conditions are as follows: source temperature 200 °C, cone voltage 4.5 kV, detector voltage 1.57 kV, nebulizing gas flow 1.5 L min^{-1}. Solvents and reagents were of analytical grade or the highest grade commercially available and were used without further purification.

2.1. Crystal structure determination

A suitable crystal for X-ray crystal structure analysis of 2-(4-methoxyphenyl)-4-[2-(4-pentylphenyl)- ethynyl]cyclopent-4-ene-1,3-dione (**8g**) was obtained by slow evaporation from ethyl acetate at room temperature. Data were collected on a Bruker Kappa APEXII CCD diffractometer using Mo Kα radiation (λ = 0.71073 Å). The structure was solved by direct methods using SIR2014 (Burla et al., 2015), and refined by full matrix least-squares on F^2 using SHELXL2014/7 (Sheldrick, 2015). All *non*-hydrogen atoms were refined anisotropically and H-atoms were placed in calculated positions (C—H = 0.93 to 0.97 Å) and were included in the refinement in the riding model approximation, with Uiso(H) = 1.2–1.5Ueq(C). The programs WinGX (Farrugia, 2012), PLATON (Spek, 2009) and ORTEP-3 for Windows (Farrugia, 2012) were also used in the study. The crystal and structure refinement data of **8g** are summarized in Table 3.

2.2. General procedure for Sonogashira coupling

1-(4-methoxyphenyl)-3-(*p*-tolylethynyl)-1*H*-pyrrole-2,5-dione (**8j**) – To a solution of 3-bromo-1-(4-methoxyphenyl)-1*H*-pyrrole-2,5-dione (**6**) (280.96 mg, 1.0 mmol, 1.0 eq) in THF (5 mL) at 0 °C under nitrogen atmosphere were added $PdCl_2(PPh_3)_2$ (35 mg, 0.049 mmol, 5 mol%), CuI (9.5 mg, 0.05 mmol, 5 mol%) and 1-ethynyl-4-methylbenzene (**7j**) (174.1 mg, 1.5 mmol, 1.5 eq) and stirred for 5 min. Then, Et_3N (1.5 eq) was added dropwise, ice bath was removed, the temperature was raised to 50 °C and the reaction was monitored by TLC. After completion, the reaction was cooled to room temperature, then quenched with ethylacetate (30 mL), and the organic phase was washed with saturated NH_4Cl (10 mL) and then dried over $MgSO_4$. Evaporation under reduced pressure followed by column chromatography on silica gel (20% ethyl acetate in hexanes) afforded the product.

3-(4-hydroxybut-1-yn-1-yl)-1-(4-methoxyphenyl)-1*H*-pyrrole-2,5-dione **(8a)**, Gummy solid; Yield (206 mg, 76%); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 2.39–2.41 (m, 2H), 3.54–3.61 (m, 5 H), 6.77 (br. s., 1 H), 6.91 (d, J = 6.78 Hz, 2 H), 7.15 (d, J = 6.00 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 25.55, 55.49, 67.94, 96.21, 108.08, 114.45 (2C), 123.92, 127.58, 129.35,

132.22 (2C), 159.11, 169.83 (2C); (+)-HRESI-MS calcd for $C_{15}H_{14}NO_4$ ($M+H^+$): 272.0923; found: 272.0925.

3-(cyclopropylethynyl)-1-(4-methoxyphenyl)-1*H*-pyrrole-2,5-dione **(8b)**, Gummy solid; Yield (221 mg, 83%); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 0.92–0.98 (m, 2 H), 1.19 (d, J = 7.16 Hz, 1 H), 1.59–1.64 (m, 2 H), 3.76 (s, 3 H), 6.76 (s, 1 H), 6.91–6.94 (m, 2 H), 7.16–7.19 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 8.80 (2C), 10.11, 54.39, 96.53, 112.77, 113.38 (2C), 122.74, 126.48 (2C), 130.39, 133.04, 158.06, 168.72 (2C); (+)-HRESI-MS calcd for $C_{16}H_{14}NO_3$ ($M+H^+$): 268.0974; found: 268.0980.

3-(hex-1-yn-1-yl)-1-(4-methoxyphenyl)-1*H*-pyrrole-2,5-dione **(8c)**, Gummy solid; Yield (183 mg, 65%); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 0.91 (d, J = 6.78 Hz, 3 H), 1.23–1.40 (m, 2 H), 1.71 (dd, J = 15.45, 6.97 Hz, 2 H), 3.45 (t, J = 6.00, 3.00 Hz, 2 H), 3.82 (br. s., 3 H), 6.96–7.45 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 12.92, 18.41, 20.77, 31.23, 55.56, 96.11, 109.72, 119.66 (2C), 125.99 (2C), 131.69 (2C), 135.62, 157.07, 171.20 (2C); (+)-HRESI-MS calcd for $C_{17}H_{18}NO_3$ ($M+H^+$): 284.1287; found: 284.1295.

3-((3-hydroxyphenyl)ethynyl)-1-(4-methoxyphenyl)-1*H*-pyrrole-2,5-dione **(8d)**, Gummy solid; Yield (271 mg, 85%); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 3.79 (br. s., 3 H), 6.81–7.46 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 55.50, 95.26, 109.16, 113.96, 113.96, 114.57 (2C), 119.37, 121.46, 123.68, 124.23, 127.61 (2C), 129.71, 136.10, 155.90, 159.93, 168.83; (+)-HRESI-MS calcd for $C_{19}H_{14}NO_4$ ($M+H^+$): 320.0923; found: 320.0930.

1-(4-methoxyphenyl)-3-((trimethylsilyl)ethynyl)-1*H*-pyrrole-2,5-dione **(8e)**, Gummy solid; Yield (179 mg, 60%); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 0.01 (s, 9 H), 3.59 (s, 3 H), 6.59 (s, 1H), 6.71–6.81 (d, J = 9.04 Hz, 1 H), 7.00 (d, J = 9.04 Hz, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 0.05, 0.56, 55.92, 96.24, 111.12, 114.92 (2C), 128.01 (2C), 129.67, 132.71, 134.57, 159.58, 170.27 (2C); (+)-HRESI-MS calcd for $C_{16}H_{18}NSiO_3$ ($M+H^+$): 300.1056; found: 300.1060.

1-(4-methoxyphenyl)-3-(phenylethynyl)-1*H*-pyrrole-2,5-dione **(8f)**, Gummy solid; Yield (242 mg, 80%); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 3.79 (br. s., 3 H), 6.77–7.49 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 55.50, 95.43, 111.59, 114.64 (2C), 121.27, 123.60, 127.56 (2C), 127.87 (3C), 129.47 (2C), 131.37 (2C), 136.31, 159.89, 171.49 (2C); (+)-HRESI-MS calcd for $C_{19}H_{14}NO_3$ ($M+H^+$): 304.0974; found: 304.0980.

1-(4-methoxyphenyl)-3-((4-pentylphenyl)ethynyl)-1*H*-pyrrole-2,5-dione **(8g)**, Colorless crystal; mp (101–102 °C); Yield (261 mg, 70%); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 0.89 (t, J = 6.00, 12.00 Hz, 3 H), 1.30–1.34 (m, 4 H), 1.60 (d, J = 7.54 Hz, 2 H), 2.61 (d, J = 7.90 Hz, 2 H), 3.82 (s, 3 H), 6.77 (s, 1 H), 6.96–6.99 (m, 2 H), 7.22–7.27 (m, 4 H), 7.50–7.53 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 14.20, 22.45, 31.46, 33.64, 37.52, 55.55, 97.21, 112.44, 114.46 (2C), 120.53, 124.88, 127.52 (2C), 130.01 (2C), 131.41, 134.20 (2C), 159.23, 171.12 (2C);); (+)-HRESI-MS calcd for $C_{24}H_{24}NO_3$ ($M+H^+$): 374.1756; found: 374.1765.

3-((6-methoxynaphthalen-2-yl)ethynyl)-1-(4-methoxyphenyl)-1*H*-pyrrole-2,5-dione **(8h)**, Gummy solid; Yield (317 mg, 83%); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 3.78 (br. s., 3 H), 3.82 (br. s., 3 H), 6.74–8.12 (m, 11 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 55.41, 55.52, 97.46, 105.29, 114.44 (2C), 117.15 (2C), 127.15, 127.81 (2C), 128.91 (2C), 128.94, 130.02, 132.18 (2C), 132.99, 134.58, 142.20, 159.05, 159.67, 167.42 (2C); (+)-HRESI-MS calcd for $C_{24}H_{18}NO4$ ($M+H^+$): 384.1236; found: 384.1240.

3-([1,1′-biphenyl]-4-ylethynyl)-1-(4-methoxyphenyl)-1*H*-pyrrole-2,5-dione **(8i)**, Gummy solid; Yield (299 mg, 79%); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 3.79 (s, 3 H), 6.81 (d, J = 8.67 Hz, 1H), 6.96 (d, J = 8.85 Hz, 2 H), 7.30–7.66 (m, 11 H), 8.03 (d, J = 8.29 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 55.53, 96.40, 114.44 (2C), 124.12, 126.29, 127.06 (8C), 128.91 (3C), 128.97, 132.18 (2C), 140.08, 142.20, 159.67, 167.40 (2C); (+)-HRESI-MS calcd for $C_{25}H_{18}NO_3$ ($M+H^+$): 380.1287; found: 380.1297.

1-(4-methoxyphenyl)-3-(p-tolylethynyl)-1*H*-pyrrole-2,5-dione **(8j)**, Yellow solid; mp (107-108 °C); Yield (291 mg, 92%); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 2.32 (br. s., 3 H), 3.78 (s, 3 H), 6.70 (s, 1 H), 7.04–7.16 (m, 4 H), 7.25–7.49 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 23.54, 55.46, 96.03, 106.06, 114.46 (3C), 123.85, 127.58 (2C), 129.21 (3C), 132.28 (2C), 133.58, 139.74, 159.19, 171.18 (2C); (+)-HRESI-MS calcd for $C_{20}H_{16}NO_3$ ($M+H^+$): 318.1130; found: 318.1142.

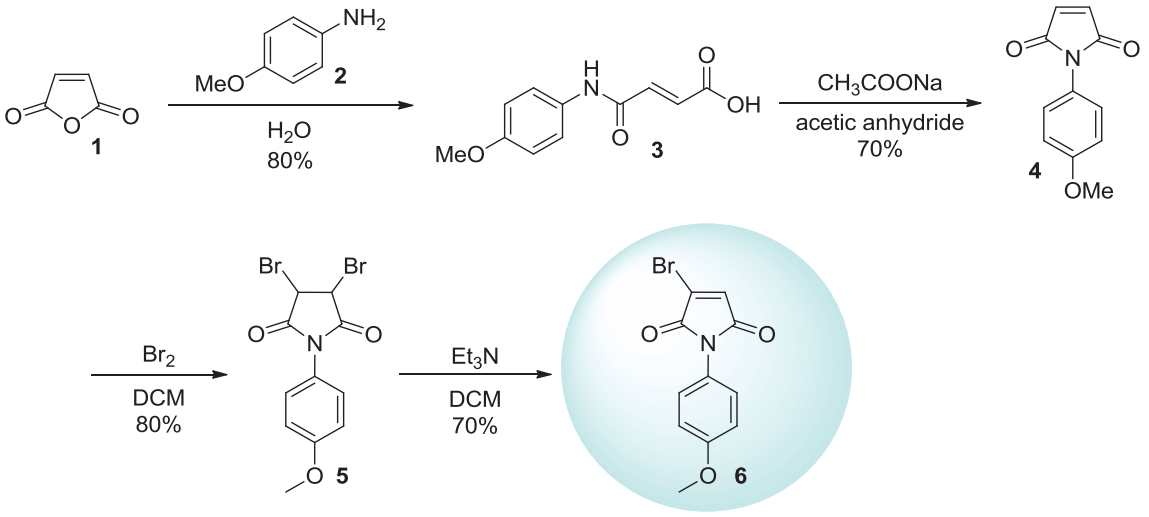
1-(4-methoxyphenyl)-3-(4-phenylbut-1-yn-1-yl)-1*H*-pyrrole-2,5-dione **(8k)**, Gummy solid; Yield (252 mg, 76%); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 2.40–3.04 (m, 4 H), 3.76 (s, 3 H), 6.77–7.40 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 18.37, 34.53, 55.54, 114.52, 127.61, 127.71, 128.39, 128.56, 128.68, 128.97, 132.28, 139.78, 141.81, 159.63, 174.67; (+)-HRESI-MS calcd for $C_{20}H_{16}NO_3$ ($M+H^+$): 332.1287; found: 332.1295.

2.3. General procedure for triazole formation

3-(1-benzyl-1*H*-1,2,3-triazol-4-yl)-1-(4-methoxyphenyl)-1*H*-pyrrole-2,5-dione (**10a**) – To a solution of 1-(4-methoxyphenyl)-3-((trimethylsilyl)ethynyl)-1*H*-pyrrole-2,5-dione (**8e**) (299.09 mg, 1.0 mmol, 1.0 eq) in THF (5 mL) at 25 °C under a nitrogen atmosphere were added benzyl azide (160 mg, 1.2 mmol, 1.2 eq) and CuI (28 mg, 0.15 mmol, 15 mol%). PMDETA (208 mg, 1.2 mmol, 1.2 eq) was followed by TBAF (1.2 eq) and the reaction was sonicated for 1 h. TLC analysis revealed no starting material. Next, the reaction was quenched with CH_2Cl_2 (20 mL) and the organic phase was washed with a saturated solution of NH_4Cl (10 mL), then dried over $MgSO_4$. Evaporation under reduced pressure followed by column chromatography provided the desired product.

3-(1-benzyl-1*H*-1,2,3-triazol-4-yl)-1-(4-methoxyphenyl)-1*H*-pyrrole-2,5-dione **(10a)**, Gummy solid; Yield (234 mg, 65%); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 3.62–3.80 (m, 5 H), 6.75–7.38 (m, 10 H) 8.33 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 55.53, 57.75, 96.57, 114.44, 119.1, 127.06 (3C), 127.50, 128.91, 130.02, 132.18 (2C), 132.99, 134.57, 159.67, 167.40 (2C); (+)-HRESI-MS calcd for $C_{20}H_{17}N_4O_3$ ($M+H^+$): 361.1300; found: 361.1312.

3-(1-(3-chlorophenyl)-1*H*-1,2,3-triazol-4-yl)-1-(4-methoxyphenyl)-1*H*-pyrrole-2,5-dione **(10b)**, Gummy solid; Yield (209 mg, 55%); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 3.66 (s, 3 H), 6.72–7.59 (m, 9 H), 8.33 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 55.51, 100.67, 114.37 (2C), 124.65, 126.49, 127.84 (2C), 127.84, 129.13 (2C), 129.45 (2C), 131.1, 131.56, 134.14, 159.59, 169.41(2C); (+)-HRESI-MS calcd for $C_{19}H_{14}ClN_4O_3$ ($M+H^+$): 381.0754; found: 381.0759.



Scheme 1 Synthesis of halomaleimide **6**.

1-(4-methoxyphenyl)-3-(1-(3-methoxyphenyl)-1H-1,2,3-triazol-4-yl)-1*H*-pyrrole-2,5-dione **(10c)**, Gummy solid; Yield (188 mg, 50%); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 3.63 (m, 3 H), 3.78 (s, 3 H), 6.77–7.76 (m, 9 H), 8.07 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 54.80, 55.58, 97.19, 106.86, 114.22 (2C), 118.67, 125.83 (2C), 126.41 (3C), 131.63, 136.47, 141.50, 154.67, 157.76 (2C), 168.9(2C); (+)-HRESI-MS calcd for $C_{20}H_{17}N_4O_4$ ($M+H^+$): 377.1250; found: 377.1254.

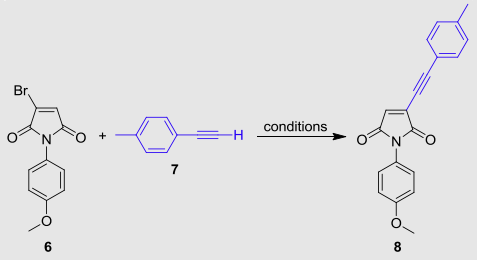
1-(4-methoxyphenyl)-3-(1-(2-nitrophenyl)-1*H*-1,2,3-triazol-4-yl)-1*H*-pyrrole-2,5-dione **(10d),** Gummy solid; Yield (203 mg, 52%); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 6.63–6.72 (m, 2 H), 6.80–6.85 (m, 2 H), 7.04–7.08 (m, 2 H), 7.32–7.39 (m, 2 H), 8.08–8.11 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 53.39, 100.38, 116.86 (2C), 118.83 (2C), 126.11(3C), 128.91 (2C), 132.21, 135.85 (2C), 144.83 (2C), 158.52, 169.20 (2C); (+)-HRESI-MS calcd for $C_{19}H_{14}N_5O_5$ ($M+H^+$): 392.0995; found: 392.1002.

3. Results and discussion

Typical Sonogashira reaction conditions involve the use of $PdCl_2(PPh_3)_2$ or $Pd(PPh_3)_4$ as the catalyst, CuI as the cocatalyst, and an excess amount of base used as the solvent. Often, an excess amount of the terminal alkyne is needed to obtain the final products in good yields with halogenated substrates.

We prepared maleimide acid **3** from maleic anhydride **1** by the treatment with amine **2** in the presence of water (Dulla et al., 2014). Thus the obtained **3** was reacted with acetic

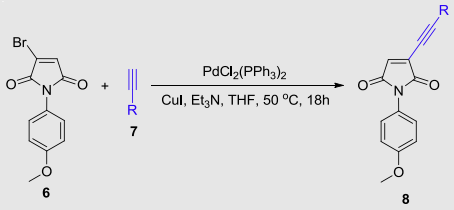
Table 1 Survey of the reaction conditions.



#	Catalyst (mol%)	Bases (eq)	Conditions (°C, h)	Solvent	Yield (%)[a]
1	$Pd(OAc)_2$ (10)	Cs_2CO_3 (2)	rt, 24	MeOH	nr
2	$Pd(OAc)_2$ (10)	K_2CO_3 (2)	rt, 24	MeOH	nr
3	$Pd(OAc)_2$ (10)	K_2CO_3 (2)	rt, 24[b]	THF:H_2O	nr
4	$Pd(OAc)_2$ (10)	Cs_2CO_3 (2)	rt, 24[b]	DMF	nr
5	$Pd(OAc)_2$ (10)/CuI (5)	Cs_2CO_3 (2)	rt, 4[b]	DMF	nr
6	$PdCl_2$(dppf) (10)	K_2CO_3 (2)	rt, 5[b]	THF:H_2O	nr
7	$PdCl_2(PPh_3)_2$ (5)/CuI (5)	Et_3N (1.5)	50, 18	THF	92
8	$PdCl_2(PPh_3)_2$ (5)	Et_3N (1.5)	50, 18	THF	40
9	CuI (5)	Et_3N (1.5)	50, 18	THF	30

[a] Isolated yield.
[b] After indicated time the temperature was adjusted to reflux and kept for 18 h.

Table 2 Sonogashira cross-coupling reaction between halomaleimide (**6**) and acetylenes (**7a–k**).



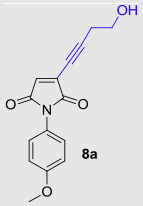
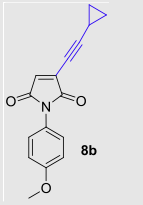
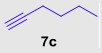
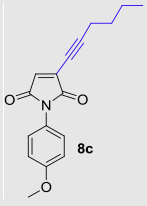
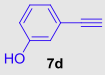
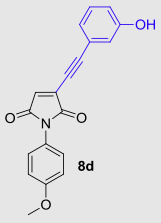
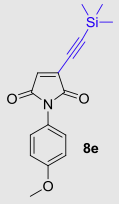
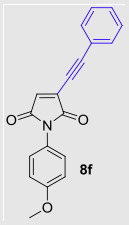
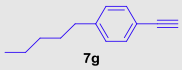
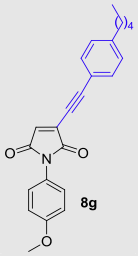
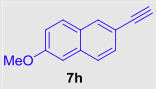
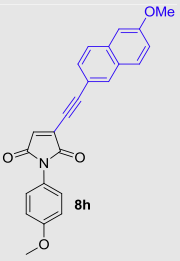
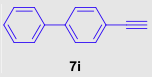
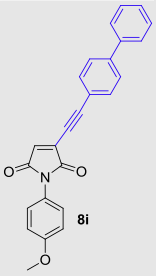
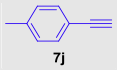
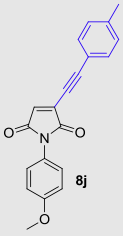
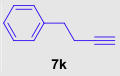
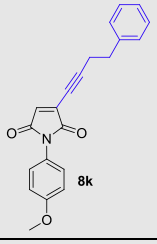
#	Acetylene	Product	Yield (%)[a]
1			76
2			83
3			65
4			85
5			60
6			80

Table 2 (*continued*)

#	Acetylene	Product	Yield (%)[a]
7	 7g	 8g	70
8	 7h	 8h	83
9	 7i	 8i	79
10	 7j	 8j	92
11	 7k	 8k	76

[a] Isolated yield.

anhydride and sodium acetate (Kaur et al., 2015) to get the cyclic maleimide **4**. This cyclic maleimide was treated with bromine to obtain the dibromo intermediate **5**, which further on treatment with triethylamine afforded the desired haloma-leimide **6** (Rulev et al., 2013) Scheme 1.

Initially, we surveyed transition metal-catalyzed cross-coupling reactions of a vinylic leaving group by a carbon nucleophile, the substitution nucleophilic vinylic (SNV) reaction, by developing a simple methodology using bases and solvents. The most representative results obtained using transition metal-catalyzed cross-coupling reactions are presented in entries 1–9 (Table 1).

When **6** was reacted with 1-ethynyl 4-methylbenzene **7** in the presence of $Pd(OAc)_2$ (10%), using Cs_2CO_3 (entry 1, Table 1) in methanol and K_2CO_3 (2 eq) in methanol and THF:H_2O, at room temperature for 24 h (entries 2–3, Table 1), the reaction did not work.

Similar conditions were also applied for refluxing the reaction mixture, but no progress was made (entries 3–4, Table 1); using CuI as a co-catalyst did not affect the reaction (entry 5, Table 1). $PdCl_2$(dppf) also did not give the acetylenic compound (entry 6, Table 1).

Using the catalyst combination of $PdCl_2(PPh_3)_2$/CuI in THF in the presence of Et_3N at room temperature the reaction

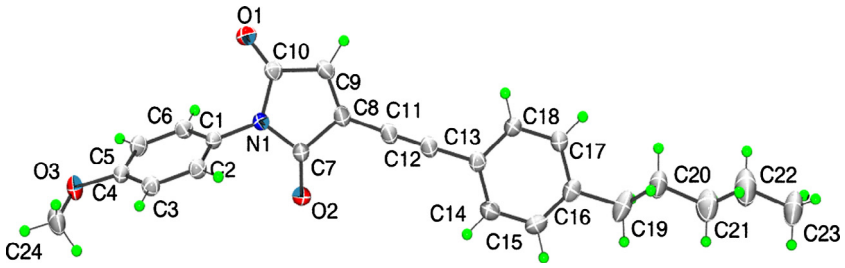


Figure 2 The molecular structure of 2-(4-methoxyphenyl)-4-[2-(4-pentylphenyl)ethynyl]cyclopent-4-ene-1,3-dione.

Table 3 Crystal data and structure refinement for **8g**.[a]

Color/dimensions (mm)	Colorless/0.20 × 0.25 × 0.3
Chemical formula	$C_{24}H_{23}NO_3$
Formula weight	373.43
Crystal system	Triclinic
Space group	*P*1
Unit cell dimensions	
a (Å)	5.3692(6)
b (Å)	9.2513(10)
c (Å)	10.3070(11)
α (°)	85.349(4)
β (°)	84.420(4)
γ (°)	86.892(4)
Volume (Å^3)	507.31(10)
Z	1
Density (calculated) (g/cm^3)	1.222
Absorption coefficient (mm^{-1})	0.080
F (000)	184
θ range for data collection (°)	1.99–25.24
Reflections measured	13205
Independent/observed reflections	4186/3355 (R_{int} = 0.024)
Data/restraints/parameters	4186/3/255
Goodness of fit on F^2	1.076
Final *R* indices [$I > 2\_(I)$]	*R*1 = 0.052, *wR*2 = 0.151
R indices (all data)	*R*1 = 0.066, *wR*2 = 0.164
Δρ max, min, (e.Å^{-3})	0.37/−0.20

[a] Crystallographic data for the structure of **8g** have been deposited with the Cambridge Crystallographic Data Centre as the Supplementary data CCDC No. 1483037. Copies of the data can be obtained free of charge via http://www.ccdc.cam.ac.UK/data request/cif, or by contacting the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1ES, UK. Fax: + 44 1223 336033.

also failed to give the desired coupling product,[6c,11a] but when temperature was elevated to 50 °C, the product was obtained in 92% yield (entry 7, Table 1). The reaction yield has proven to be dependent upon the presence of both catalysts, palladium and copper, whereas when used separately, only copper or palladium, the desired product was obtained in only 40% and 30% of isolated yields (entries 8 and 9, Table 1).

Having found the best conditions, to further investigate their catalytic role, $PdCl_2(PPh_3)_2$ and CuI were used alone, giving poor yields (40% and 30%, respectively, entries 8–9, Table 1), which indicates that the mixture of catalysts (entry 7, Table 1) at 50 °C and Et_3N has prime importance in the coupling of acetylene with halomaleimide in our synthetic strategy.

As shown in Table 2, several aliphatic and aromatic alkynes (**7**) were found to react smoothly with halomaleimide **6** in the presence of $PdCl_2(PPh_3)_2$/CuI in THF, and the desired products **8a**–**k** were obtained in yields (entries 1–11) ranging from 60% to 92%.

It was found that the reaction carried out with alkyl alkynes worked well to produce 76% and 65% yields (Table 2, entries 1 and 3), and showed that 3-butyne-1-ol gives moderate yields (Table 2, entry 1). Cyclopropene resulted in a good yield of 83% (Table 2, entry 2). Similarly, trimethylsilyl alkyne yielded 60% (Table 2, entry 5).

Generally, coupling reactions with alkyl acetylenes yielded the expected products in moderate yields (Table 2, entries 2 and 3). For aryl alkynes, the product yield depended on the substitution pattern of the phenyl ring. Arylacetylenes having electron-rich moieties gave better yields (85% and 83%; Table 2, entries 4 and 8) than other alkynes (70–80%, respectively; Table 2, entries 6, 7 and 9). A crystal of **8g** was obtained by slow evaporation from ethyl acetate at room temperature.

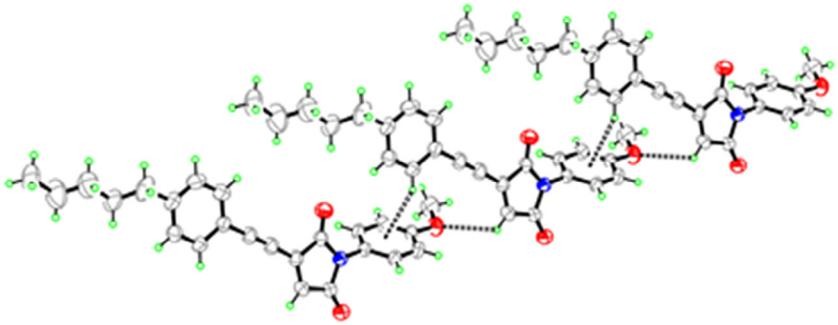
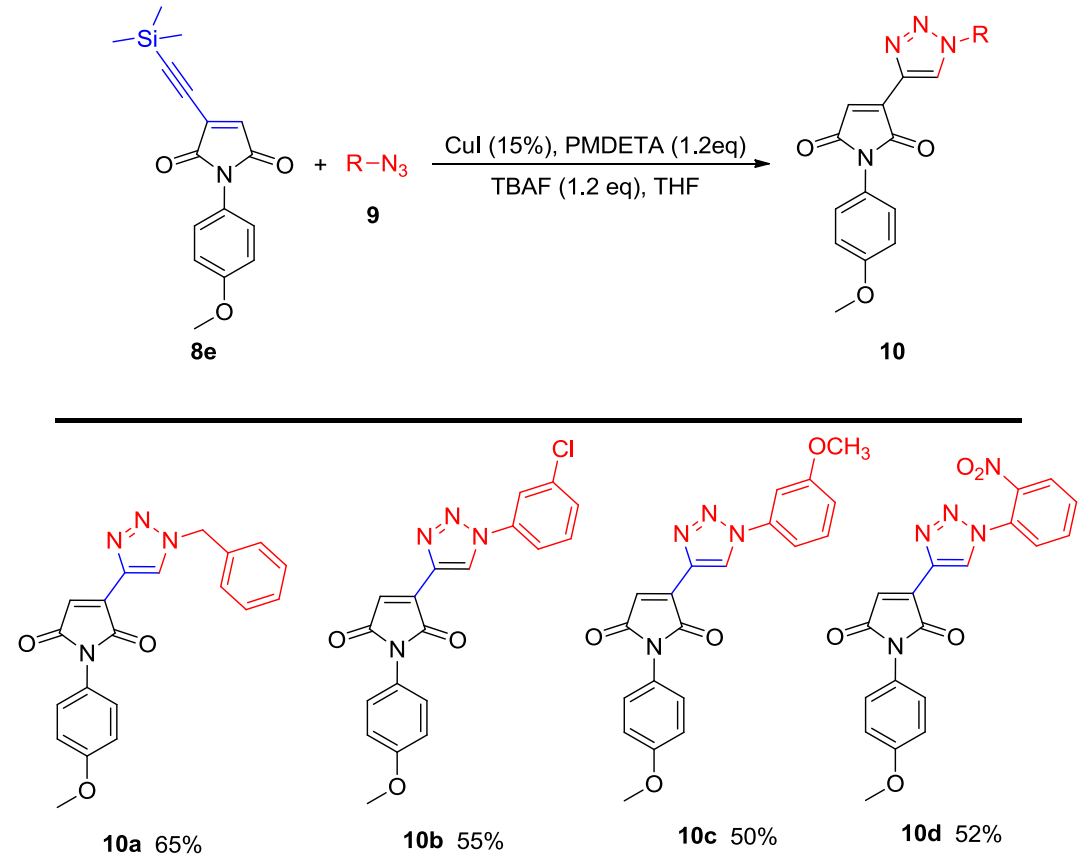


Figure 3 Crystal packing in **8g** showing the C–H···O and C–H···π interactions.



Scheme 2 Synthesis of 1,2,3-triazole rings from alkynyl maleimide **(8e)** (Isolated yield.).

*3.1. X Crystal structure analysis of **8g***

The molecular structure of **8g** is shown in Fig. 2 together with the atom-labeling scheme. The crystal and structure refinement data are collated in Table 3. The cyclopent-4-ene-1,3-dione ring makes a torsion angle with the phenyl ring attached to it of 64.46(11)° being almost coplanar with the other one [dihedral angle = 6.08(14)°]. In the crystal the three-dimensional architecture is stabilized by intermolecular C–H···O (H9···O3^{i} = 2.82 Å, C9–H9···O3 = 111°; symmetry operation $i = x, y\ 1 + z$) and C–H···π [H18···Cg(C1–C6)^{i} = 2.95 Å, C18–H18···Cg(c1–C6)^{i}; symmetry operation $i = x, y\ 1 + z$) interactions, as seen in Fig. 3.

As a concern regarding the synthetic utility of general synthesis of 1-(4-methoxyphenyl)-3-((trimethylsilyl)ethynyl)-1*H*-pyrrole-2,5-dione (**8e**), different azides were reacted in order to obtain 1,2,3-triazoles. The conducted reactions provided the desired products in good yield, similar to the methodology developed earlier by our group (Scheme 2).

4. Conclusion

In summary, we have described a simple method where bromomaleimide undergoes a cross-coupling reaction under the Sonogashira conditions with acetylenes in the presence of $PdCl_2(PPh_3)_2$/CuI catalysis. The alkynyl maleimides were obtained in good to very good yield range. The alkynylated products were then subsequently converted into the corresponding 1,2,3-triazoles via a click chemistry approach in moderate yields. This simple approach may find interest in the development of small molecules incorporating triazoles. The crystal structure of **8g** showed that the five membered ring makes a torsion angle with the phenyl ring attached to it of 64.46(11)° being almost coplanar with the other one. The molecules are arranged in the crystal in layers parallel to *z* through C–H···O and C–H···π interactions.

Acknowledgments

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