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Cyclization and rearrangement products from coupling reactions between terminal *o*-alkynylphenols or *o*-ethynyl(hydroxymethyl)benzene and 6-halopurines

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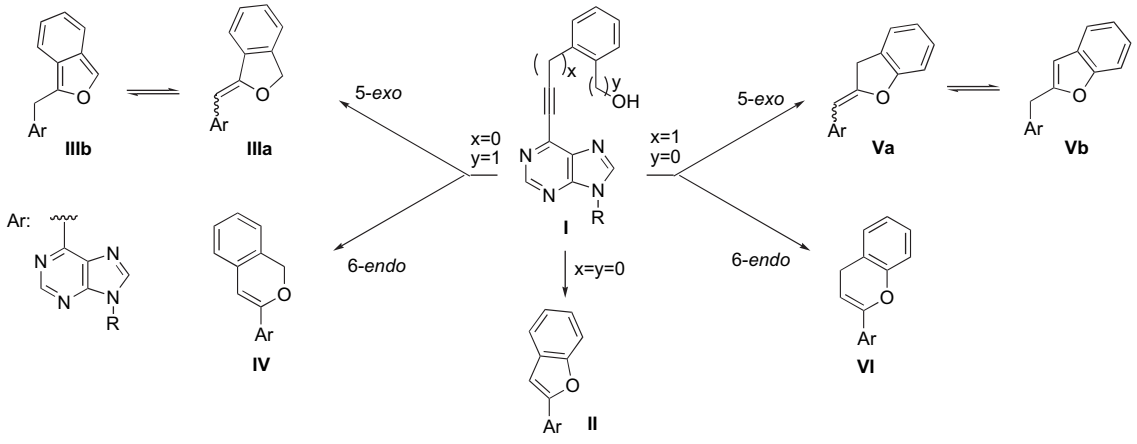
Abstract—Cyclization reactions on 6-[(2-hydroxyphenyl)ethynyl]purines, 6-[(2-hydroxymethylphenyl)ethynyl]purines and 6-[(2-hydroxyphenyl)propyn-1-yl]purines have been studied. 6-(2-Benzofuryl)purines are readily available via a one-pot Sonogashira coupling–cyclization between 6-iodopurine and 2-ethynylphenol. When the same reaction was performed with *o*-(hydroxymethyl)ethynylbenzene, 6-[isobenzofuran-1(3*H*)-ylidenemethyl]purine was formed, mainly as the (*E*)-isomer. Acid catalyzed isomerization of the (*E*)-compound afforded the (*Z*)-isomer. The latter compound was also formed from a two-step reaction; Sonogashira coupling with *O*-silylated alkyne followed by deprotection and subsequent 5-*exo* cyclization. Sonogashira coupling between 6-halopurines and 2-propynylphenol gave only the alkyne coupling product and no cyclization took place. However, the Sonogashira product was unexpectedly rearranged to 6-(3-phenoxypropa-1,2-dienyl)purines under basic conditions. Theoretical calculations demonstrated that the allenes are more stable than their alkyne isomers.

1. Introduction

During our synthetic studies toward potential plant growth hormone analogs,[1] we found that 6-(hydroxyalkynyl)purines ring close by an *exo-dig* attack from the hydroxy group on the triple bond.[1d] The electron deficient purine activates the alkyne function for nucleophilic attack. We have previously studied addition of nucleophiles to alkenylpurines.[2] Purines carrying different carbon substituents in the 6-position are associated with a wide variety of biological effects, like antimycobacterial activity,[3] cytotoxic effects,[4] a(nta)-gonist activity toward adenosine receptors,[5] inhibition of 15-lipoxygenase,[6] and antiviral activity[7,4f] in addition to the above-mentioned ability to stimulate plant growth.[1] In order to increase the synthetic methodologies for constructing 6-substituted purines, we decided to study the cyclizations of alkynylpurines with the general structure **I** and to explore the possibility of forming benzofuryl derivatives **II**, **III**, and **V** by 5-*exo* cyclization, or isomeric 6-*endo* products **IV** and **VI** (Scheme 1).



Scheme 1. Cyclization reactions studied herein.

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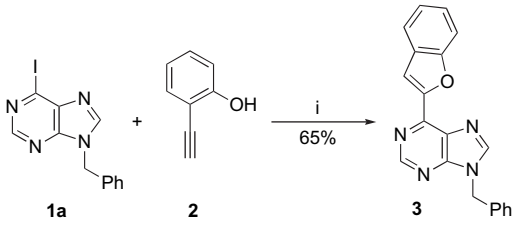
2. Results and discussion

Benzo[*b*]furans and indoles may be formed by Pd(0) and/or Cu(I)-mediated reactions of 2-alkynylphenols.[8] 2-Aryl- or 2-vinylbenzo[*b*]furans have been prepared by a one-pot Sonogashira coupling–cyclization when ethynylphenol **2** was reacted with aryl- or vinyl iodides under solventless microwave-enhanced Sonogashira coupling conditions, but only moderate yields were achieved due to polymerization reactions.[9] The 6-(2-benzofuryl)purine **3** (Scheme 2) exhibits antimycobacterial activity and has previously been prepared by Stille coupling on 6-halopurine.[3d] 6-(2-Benzofuryl)purine riboside has been prepared by Suzuki coupling in quite modest yield.[4f] We have determined that 6-iodopurine **1a** reacts with ethynylphenol **2** under standard Sonogashira conditions to give 2-benzofurylpurine **3** in a yield almost identical to what have been obtained previously,[3d] but the reaction described herein takes place under more environmentally benign conditions and utilizes less expensive starting materials, since the use of an organotin compound in stoichiometric amounts is avoided (Scheme 2).



Scheme 2. Reagents and conditions: (i) $(Ph_3P)_2PdCl_2$, CuI, $(i\text{-Pr})_2NH$, DMF, 60 °C.

6-Iodopurine **1a** was reacted with terminal alkynes **4**. When the acetylene carried a free hydroxy group (**4a**), cyclization took place under Sonogashira conditions and the (*E*)-5-*exo* product **5** was formed together with minor amounts of the (*Z*)-isomer **7** (Scheme 3). NMR spectroscopic analyses indicated that compound **5** exists as an enol ether with the CH_2-group inside the newly formed ring, and the presence of an aromatic benzo[*c*]furyl substituent (product type **IIIb**, Scheme 1) could easily be excluded. Also other studies of 2-alkylbenzo[*c*]furans have shown that equilibria like **IIIa**–**IIIb** (Scheme 1) lies in favor of the benzenoid tautomer **IIIa**.[10]

Structure elucidation of compound **5** was initially based on NOESY correlation between H-2 in the purine ring and one of the hydrogens in the benzofuryl substituent (Scheme 3). The distance between the H-2 and the benzene ring would have been much larger in the (*Z*)-isomer **7** or in the 6-*endo* cyclized isomer (comp. **IV**, Scheme 1).

It was interesting to note that the chemical shift for the benzofuryl proton correlating to H-2 in the NOESY spectrum was shifted significantly downfield (δ 9.84 ppm). This might be explained by the close proximity to N-1 in the purine. The only difference found in the ^1H–^{15}N HMBC spectra of compound **5** and isomer **7** (Scheme 3) discussed below was a correlation between N-1 and the proton shifted downfield in the benzofuran ring of compound **5**. This confirms the close proximity of those two atoms and a hydrogen bond between them forming a pseudo 7-membered ring (Fig. 1). Not only is the hydrogen shifted downfield, also a 5.8 ppm up-field shift was observed for N-1 in compound **5** relative to the N-1 shift in the isomer **7**. The chemical shift values found for N-3, N-7, and N-9 in the two isomers were virtually identical. To the best of our knowledge, a persistent C–H···N bond in solution, detected by ^1H–^{15}N HMBC spectroscopy, has not been reported before, but it is now established that scalar couplings can be observed across H-bonds.[11] The correlation between N-1 and the benzofuryl signal at 9.84 ppm,

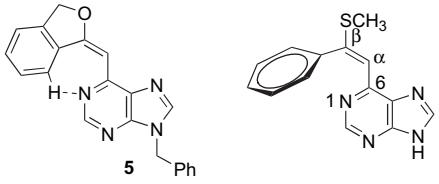
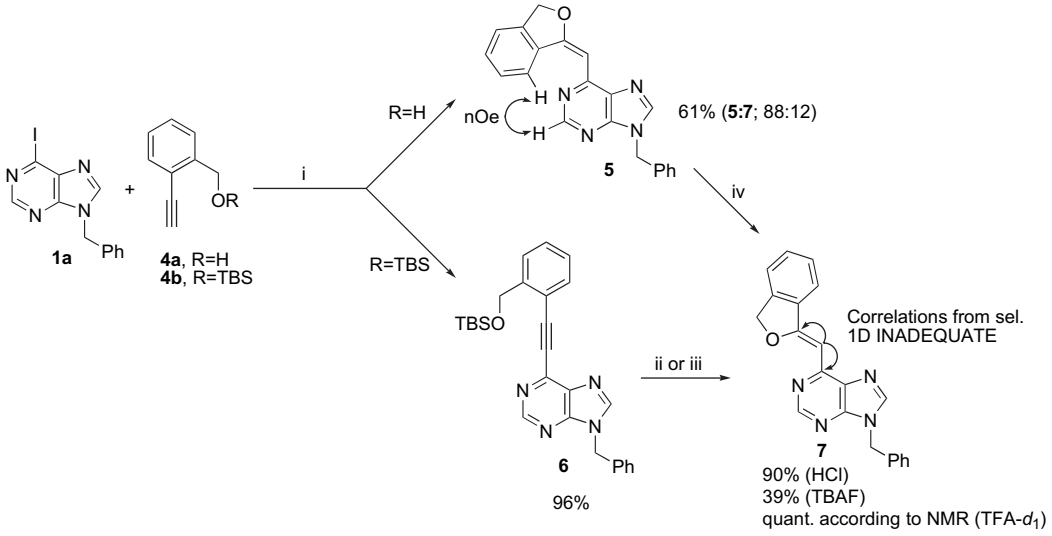


Figure 1. Structure of compound **5** with an intramolecular C–H···N bond and the more flexible 6-styrylpurine[13] where no intramolecular H-bond was observed.



Scheme 3. Reagents and conditions: (i) $(Ph_3P)_2PdCl_2$, CuI, $(i\text{-Pr})_2NH$, DMF, 60 °C; (ii) HCl (aq), EtOH; (iii) TBAF, THF; (iv) TFA-d_1, $CDCl_3$.

seen in the ^{1}H–^{15}N HMBC spectrum of compound **5**, is a strong indication of a C–H···N bond, which may be the reason for the high chemical shift value for the benzofuryl proton.

The (*E*)-benzofurylalkylidene compound **5** readily isomerizes to the corresponding (*Z*)-isomer **7** (see below) and the intramolecular H-bond appears to be a consequence of the rigidity of compound **5**. No abnormalities in the ^{1}H NMR spectra indicating a C–H···N bond could be seen in spectra reported for a series of 6-styrylpurines[12] where there is free rotation between the phenyl and double bond. In the 6-styrylpurine shown in Fig. 1, the torsion angle N1–C-6–Cα–Cβ was only 6.7° in the crystal structures, but the angle between the phenyl and purine ring was 117°.[13]

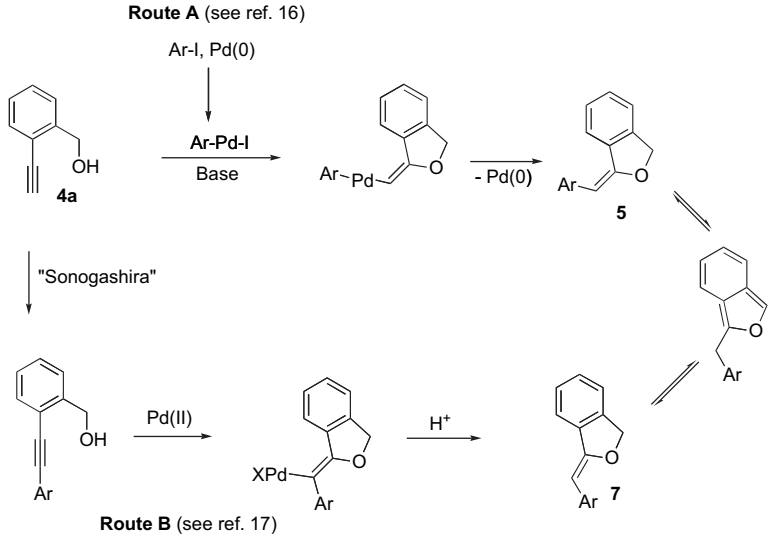
When the TBS-protected alcohol **4b** was employed in the Sonogashira reaction, the alkyne **6** was isolated in nearly quantitative yield (Scheme 3). Cyclization took place during deprotection. Both acidic and TBAF mediated cleavage of the silyl ether gave the (*Z*)-5-*exo* cyclized product **7**. The regioselectivity in cyclizations of compounds related to the general structure **I** (*x*=0, *y*=1, Scheme 1) is difficult to predict. Under basic conditions the alkoxy anion generally attacks the triple bond in related non-purine compounds to form 5-*exo* products,[14] but there are examples of rearrangement to the 6-*endo* isomer during work-up.[14a] Ring formation in the presence of TBAF appears to be sensitive to sterical hindrance; with relatively bulky alkyls on the alkyne the 6-*endo* product is formed, otherwise 5-*exo* cyclization is favored.[15] PdI_2 also promotes cyclization of alkynes related to **I** (*x*=0, *y*=1, Scheme 1). In these reactions the regiochemical outcome is sensitive to the solvent used.[16]

The ^{1}H–^{15}N HMBC spectrum, optimized for 10 Hz $^{2}J/^{3}J$ couplings of compound **7** was, with exception of the intramolecular H-bond in compound **5**, identical with the ^{1}H–^{15}N HMBC spectrum of the (*E*)-isomer **5**. In both spectra correlation between the CH═ in the side chain and N-1 was easily seen, an indication that both compounds were 5-membered rings, and that the theoretically possible 6-*endo* cyclized isochromene (type **IV** product; Scheme 1) was not formed. Selective 1D INADEQUATE (SELINQUATE) NMR, optimized for ^{1}J(C,C) proved unambiguously the 5-membered ring structure of compound **7**. When the *C*H═ in the side chain was irradiated, correlations to the two neighboring carbons, C-6 in the purine and the ═*C*–O, in the newly formed ring was observed (Scheme 3).

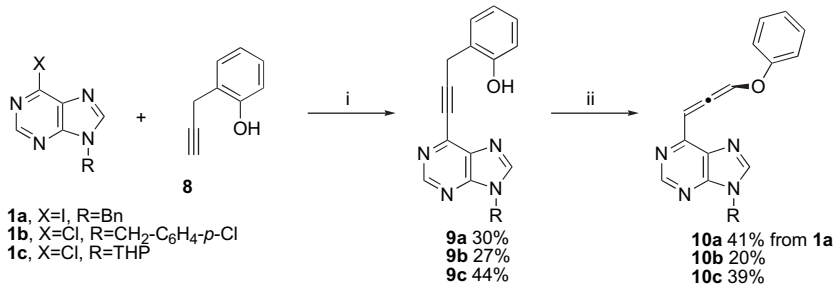
Based on the mechanism proposed for cycloisomerization of 2-alkynylbenzyl alcohols[16,17] and the isomerization experiments described below, it seems reasonable that compound **5** is formed by cyclization followed by cross-coupling (Scheme 4, route A) rather than the alternative route B. The latter route may explain the formation of the by-product **7** (Scheme 4), but compound **7** is also available from isomerization of the (*E*)-isomer **5**. CuI was present in the synthesis of compound **5**. The copper salt is of course required in the Sonogashira coupling in route B, and may replace Pd(II) in the cyclization in route B, but the possible role of CuI in route A is not clarified.

Complete isomerization of compound **5** to isomer **7** was observed in less than 5 min by NMR spectroscopy, when a drop of TFA-d_1 was added to a $CDCl_3$ solution of pure (*E*)-isomer **5**. The isomerization of pure (*E*)-**5** also took place, although slowly, in pure $CDCl_3$. After one day 8% of the (*Z*)-isomer **7** was formed and after 26 days 87% of compound **7** was present in the mixture as judged by ^{1}H NMR. In CD_2Cl_2 and CD_3OD, the conversion of compound **5** to isomer **7** was 53 and 62%, respectively, after 26 days. The (*Z*)-compound **7** was completely stable under acidic conditions. The elusive *o*-quinonoid tautomer of compounds **5** and **7** shown in Scheme 4, could not be observed in the NMR spectra from the isomerization studies, and related *o*-quinonoid isobenzofurans are reported to be highly unstable.[10]

Compounds **5** and **7** were tested as antimycobacterials and both isomers exhibited MIC values of 6.25 μg/mL against *Mycobacterium tuberculosis*. Compound **5** may have isomerized to isomer **7** during determination of antibacterial effect. The activity against *M. tuberculosis* found for compound **7** is



Scheme 4. Possible mechanisms for the formation of the isomers **5** and **7**.



Scheme 5. Reagents and conditions: (i) $(Ph_3P)_2PdCl_2$, CuI, $(i\text{-}Pr)_2NR$, DMF, 60–80 °C; (ii) CuI, Et_3N, Δ.

comparable with that reported for the benzofuryl derivative **3**,[3d] but none of these compounds are as active as our most promising antimycobacterial purines.[3]

The alkyne **8** (Scheme 5) is reported to react with aryl iodides in the presence of BuLi and a Pd(II) precatalyst to give 5-*exo* products (type **V**, Scheme 1), a reaction somewhat like route B in Scheme 3.[17] However, the application of these conditions in reaction between halopurine **1c** and the acetylene derivative **8** was not successful. Compound **9c** was prepared in moderate yield by standard Sonogashira conditions and several unsuccessful attempts were made to cyclize this compound. When refluxed in Et_3N in the presence of catalytic amounts of CuI and $(Ph_3P)_2PdCl_2$, still no cyclization occurred, but an unexpected rearrangement to the allene **10c** took place. We found that the reaction took place in Et_3N without any additives, but the yield of compound **10c** was somewhat higher when the reaction was carried out in the presence of CuI. Addition of a Pd-catalyst [generated from Pd(II) or Pd(0)] actually had a negative effect on the yield of allene. Compound **10c** was isolated in 39% when **9c** was refluxed in Et_3N in the presence of catalytic CuI. Allenes **10a** and **10b** were formed by the same reaction sequence. Compound **10a** could also be isolated directly from the Sonogashira coupling after prolonged reaction time. Allenes **10** decomposed when exposed to light in $CHCl_3$ solution and the low stability of the allenes may explain the only moderate isolated yields. The allenes **10** carry both an electron withdrawing and an electron donating group and high reactivity has also been previously reported for 'push–pull' substituted allenes.[18]

NMR spectroscopy as well as synthesis by a different route (see Scheme 7 below) confirmed the unexpected allene structure of compounds **10**. Compound **10c** possesses a mono substituted benzene ring and the ^1H and ^{13}C NMR signals (see Section 4) for the benzene ring indicated that an RO– substituent was connected to the phenyl ring. The phenoxy- and purinyl moieties were separated by a CH–C–CH linkage. Furthermore, the direct coupling constants between C and H in this fragment were found to be ca. 175 Hz, a strong indication that both CH carbons are sp^2 hybridized and that the phenyl- and purine rings were separated by the allenyloxy fragment. It is worth mentioning that 'unusual' ^{13}C NMR shifts were observed especially for the central allene carbon and C-2, C-4, and C-6 in the purine ring, all these ^{13}C resonances were shifted considerably up-field (Fig. 2). Up-field shifts for central allene carbons have been observed before when the allene carries alkoxy group(s) acting as π-donors.[18] However, the low up-field shifts found for several purine carbon resonances indicate that the purine ring behaves as a π-acceptor, which should lead to a deshielding of the central allene carbon. In 'push–pull' substituted allenes described before, the effects from the donors and acceptors often cancel each other with respect to the ^{13}C NMR shift of the central allene carbon.[18]

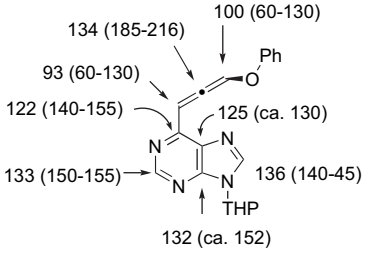
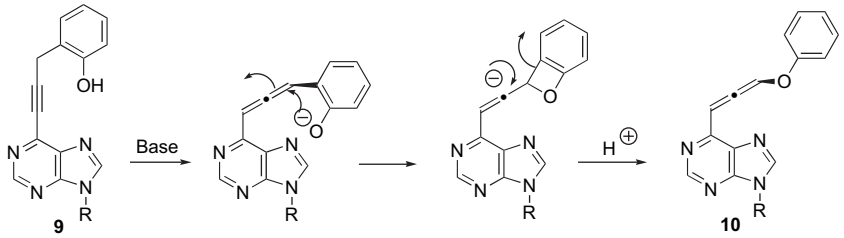
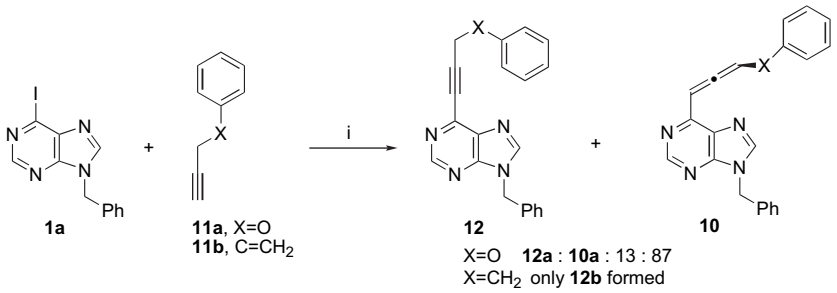


Figure 2. Structure of the phenoxy allene **10c**. Selected ^{13}C NMR shifts for compound **10c** are shown, typical shift ranges for purine ring carbons in 6-alkenyl or alkynylpurines,[1,2,6] and allene carbons[18] are shown in brackets.

A tentative mechanism for allene formation without CuI, is detailed in Scheme 6. The presence of a 4-membered ring intermediate seems reasonable given that the carbon–oxygen bond is formed by attack from the phenolate anion on an allene isomer of **9**, even though allenes are normally attacked



Scheme 6. Tentative mechanism for the formation of compounds **10**.



Scheme 7. Reagents and conditions: (i) $(Ph_3P)_2PdCl_2$, CuI, $(i\text{-Pr})_2NR$, DMF, 60 °C.

by nucleophiles at the central carbon. The favorable influence of CuI on the rearrangement is currently not understood.

In order to further confirm the structure of the allenes **10**, purine **1a** was reacted with the alkyne **11a** and the allene **10a** was isolated together with the alkyne **13a** (13%) after chromatography (Scheme 7). Theoretical calculations have shown that an alkoxy group will stabilize an allene,[19] and propargyl ethers can be isomerized to alkoxyallenes under basic conditions, but generally strong bases like Bu^{t}OK or RLi, are employed.[20] Formation of the allene **10a** under moderately basic Sonogashira conditions indicates that the 6-purinyl moiety facilitate allene formation. When the 3-phenoxypropyn-1-yl functionality was introduced in the less electron deficient purine 2-position, the expected alkyne was formed.[21]

Electronic structure calculations were carried out to further investigate the formation of the allene **10a**, rather than the expected alkyne **12a**, in Scheme 7. First, the reactants **1a** and **11a** were optimized individually before assembling the two products **12a** and **10a** from these fragments. As both the resulting compounds are highly flexible, a thorough search of the conformational space was necessary. The equilibrium structures and the gas-phase molecular energies were determined by locating the global minimum of the potential energy surface (PES) of each isolated product. A large number of starting geometries were generated, and subsequently optimized, by systematically rotating key dihedral angles in the two product structures. For compound **12a** nine conformers were found, whereas a total of 15 different conformers were found for compound **10a**. Frequency calculations were then carried out for the handful of conformers of each system possessing the lowest energy, serving both to verify that the geometries indeed corresponded to stable structures and to estimate the zero-point vibrational energy of each system. The two equilibrium structures are shown in Figure 3, and it was found that the molecular energy of the allene **10a** is 27 kJ/mol lower than the expected Sonogashira alkynylation product **12a**. By adding the zero-point vibrational energy, the energy difference increases very

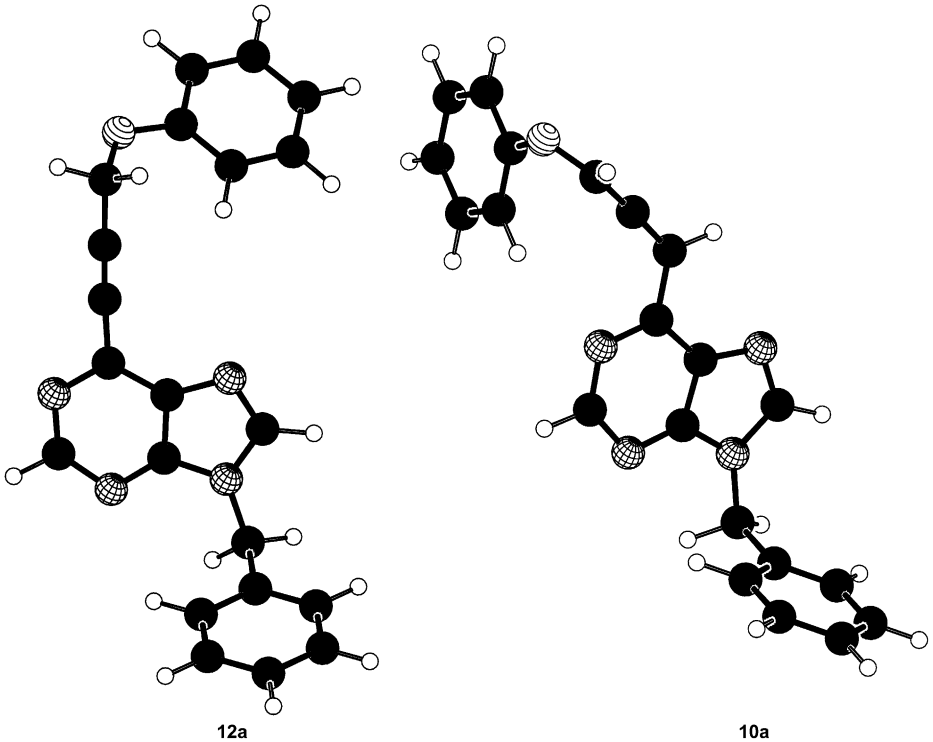
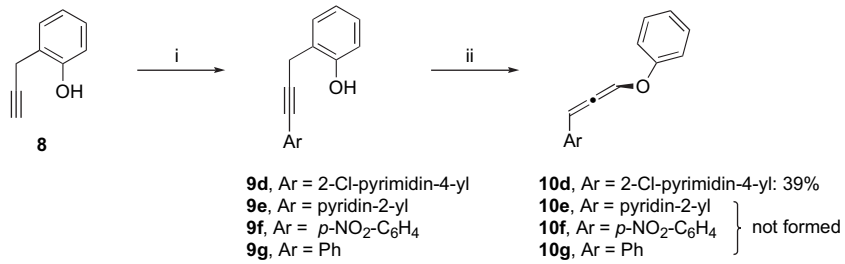


Figure 3. The gas-phase equilibrium structure of the expected Sonogashira product **12a** and the observed product **10a** as calculated at the B3LYP/6-31G(d,p) level of theory. Carbon, hydrogen, nitrogen, and oxygen atoms are shown in black, in white, with grids, and with lines, respectively.

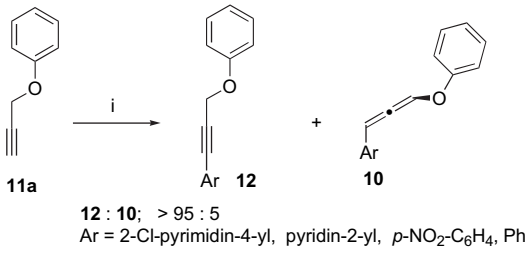


Scheme 8. Reagents and conditions: (i) ArX, $(Ph_3P)_2PdCl_2$, CuI, $(i\text{-}Pr)_2NR$, DMF, 60 °C; (ii) CuI, Et_3N, Δ.

slightly to 28 kJ/mol. One may also estimate the standard enthalpy of formation for the two compounds, and the allene is again found to be 28 kJ/mol more stable than the alkyne. While not yielding a huge energy difference, the theoretical calculations clearly indicate that of the two compounds, the allene is energetically favorable. The theoretical results are thus in very good agreement with the experimental findings.

The rearrangement of compounds **9** to the allenes **10** (Scheme 5 above) was highly unexpected and we decided to look into the scopes and limitations of the reaction. Even though allenes often has been regarded as chemical curiosities, they may be useful synthetic intermediates[22,23] and there are quite a few examples of pharmacologically active allenes including allene natural products.[24] Our hypothesis was that the allene formation is especially favorable when the allene carries both powerful electron withdrawing and electron donating groups. Coupling between purine **1a** and alkyne **11b** gave only the alkyne **12b** (Scheme 7). The alkyne **8** was reacted with different aryl halides or heteroaryl halides to give compounds **9d**–**9g**. Only the alkyne **9d** rearranged to the allene under basic conditions confirming that a highly electron withdrawing group is required for the reaction to take place (Scheme 8).

Finally, we reacted alkyne **11a** with the same aryl- or heteroaryl halides as used in the reactions described in Scheme 9. In all cases examined the 'normal' Sonogashira product **12** was formed and no allenes **10** could be detected, not even in the synthesis of pyrimidine **12d** even though the allene **10d** could be formed by rearrangement (Scheme 8).



Scheme 9. Reagents and conditions: (i) ArX, $(Ph_3P)_2PdCl_2$, CuI, $(i\text{-}Pr)_2NR$, DMF, 60 °C.

3. Conclusions

6-(2-Benzofuryl)purines are readily available by one-pot Sonogashira coupling–cyclization between 6-iodopurine and 2-ethynylphenol. When the same reaction is performed with *o*-(hydroxymethyl)ethynylbenzene, 6-(isobenzofurylidenemethyl)purine was formed, mainly as the (*E*)-isomer. The pure (*Z*)-isomer was available from a two-step reaction; Sonogashira coupling with *O*-silylated alkyne followed by acidic or TBAF mediated deprotection and subsequent 5-*exo* cyclization. The less stable *o*-quinonoid tautomer 6-(isobenzofurylmethyl)purine could not be detected, neither could formation of a 6-*endo* cyclized isochromene product. In the (*E*)-isomer of the 6-(isobenzofurylidenemethyl)-purine, NMR spectroscopy indicates the presence of an intramolecular C–H···N bond between N-1 in the purine and H-7 in the isobenzofurane.

Sonogashira coupling between 6-halopurines and 2-propynylphenol gave only the alkyne coupling product and no cyclization took place. However, the Sonogashira product was unexpectedly rearranged to 6-(3-phenoxypropa-1,2-dienyl)-purines, when refluxed in Et_3N. The yields were somewhat improved in the presence of CuI. Only allenes with both a powerful electron withdrawing and electron releasing substituent on the allene fragment was formed by this novel rearrangement.

4. Experimental

4.1. General

The ^1H NMR spectra were acquired on a Bruker Avance AV 600 spectrometer, a Bruker Avance DRX 500 spectrometer, a Bruker Avance DPX 300 spectrometer or a Bruker Avance DPX 200 spectrometer at 600, 500, 300 or 200 MHz, respectively. The ^1H decoupled ^{13}C NMR spectra were recorded at 150, 125, 75 or 50 MHz using the above-mentioned spectrometers. Assignments of ^1H and ^{13}C resonances are inferred from 1D ^1H NMR, 1D ^{13}C NMR, APT, DEPT and/or from 2D NMR (gs-COSY, gs-HMQC, gs-HMBC, NOESY) spectral data. ^{15}N NMR data were acquired at 50 MHz on the Bruker Avance DRX 500 with a 5 mm TXI ($^1H/^{13}C$, ^{15}N–^2H) Triple Resonance Inverse probe, equipped with Z-gradient coil, by applying 2D NMR experiments based on gradient pulse selection and inverse detection methods: gs-[^1H, ^{15}N] HMBC, optimized for $^2J/^3J$ $^{15}N/^1H$-couplings of 10 Hz (Bruker pulse program: *inv4gplplrndqf*, ^{15}N-pulses via F2-channel, relaxation delay, *d*1: 1.5 s, acquisition time, aq: 0.17 s, delay for evolution of long range couplings, *d*6: 0.1 s). ^{15}N chemical shifts are reported relative to external $Me^{15}NO_2$ at 0 ppm ($MeNO_2$ dissolved in the respective deuterated solvent in ratio 9:1). The selective 1D INADEQUATE (SELINQUATE) spectrum for verification of

the 5-membered ring structure of product **7** was acquired on the Bruker Avance AV 600 with a 5 mm CP–TCI ($^{1}H/^{13}C$, ^{15}N–^{2}H) Triple Resonance Inverse Cryo probe (cold ^{13}C coil and preamplifier). In order to decrease the relaxation times especially for the quaternary ^{13}C atoms and thereby to reduce the experiment time, 130 mg of product **7** was dissolved in 0.6 mL nonafluoro-*tert*-butyl alcohol (perfluoro-tertiarybutanol, 'artificial blood').[25] 5% DMSO-d_6 was added for the lock and the solution was saturated with oxygen at room temperature. Bruker pulse program: *selina*. A Gaussian shape cascade with 1024 data points (*SPNAM1*: Q5.1000) of 10 ms length (*p11*) and 32 dB attenuation (*sp1*, which was calibrated for our specific spectrometer probe), corresponding to 90° excitation was used as the ^{13}C transmitter soft pulse. The acquisition was optimized for ^{1}J(C,C) couplings of 60 Hz (*CNST3*), corresponding to $d4$=4.17 ms. Relaxation delay ($d1$): 4 s, acquisition time (aq): 0.3 s. The experimental time was 62 h with 50,000 scans applied. IR spectra were recorded at a Perkin–Elmer Spectrum One instrument. MS spectra under electron impact conditions were recorded with a VG Prospec instrument at 70 eV ionizing voltage and are presented as *m/z* (% rel int.). CH_4 was employed as the ionization gas for chemical ionization (CI). Electrospray MS spectra were recorded with a Bruker Apex 47e FT-ICR mass spectrometer. Elemental analyses were performed by Ilse Beetz Mikroanalytisches Laboratorium, Kronach, Germany. Melting points are uncorrected. DMF, CH_2Cl_2, triethylamine, and diisopropylamine were distilled from CaH_2. The following compounds were prepared by literature methods: **1a**,[26] **1b**,[3c] **1c**,[27] **2**,[9] **4b**,[28] **8**.[29] All other reagents were commercially available and used as received. All quantum chemical calculations were performed using Gaussian 03.[30] Both geometry optimizations and frequency calculations were carried out at the DFT level of theory, employing the B3LYP-functional in conjunction with the 6-31G(d,p) basis set and the 'ultrafine' grid. The chosen computational method is well established and it gives sufficiently accurate results for this study at a reasonable computational cost. Antimycobacterial activities were determined as described before.[3]

4.1.1. 6-(2-Benzo[*b*]furyl)-9-benzyl-9*H*-purine (3). Diisopropylamine (848 μL, 6.00 mmol) was added to a stirred solution of 9-benzyl-6-iodo-9*H*-purine (336 mg, 1.00 mmol), $(PPh_3)_2PdCl_2$ (35 mg, 0.05 mmol), and CuI (19 mg, 0.10 mmol) in DMF (5 mL). The mixture was heated at 60 °C, and 2-ethynylphenol (142 mg, 1.20 mmol) in DMF (1 mL) was added over 2 h and the reaction mixture was stirred for additional 3 h before evaporation. The product was isolated by flash chromatography on silica gel eluting with EtOAc–$CHCl_3$ (1:9); yield 211 mg (65%) off-white crystalline solid, mp 200–202 °C (lit.[3d] 202–203 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.08 (s, 1H, H-2), 8.29 (s, 1H, H-3 in benzofuryl), 8.13 (s, 1H, H-8), 7.70–7.72 (m, 2H in Ar), 7.28–7.40 (m, 7H, Ar), 5.48 (s, 2H, CH_2).

4.1.2. (*E*)-9-Benzyl-6-[isobenzofuran-1(3*H*)-ylidenemethyl]-9*H*-purine (5). 9-Benzyl-6-iodo-9*H*-purine **1a** (336 mg, 1.00 mmol) was added to a stirred solution of $(PPh_3)_2PdCl_2$ (35 mg, 0.05 mmol), CuI (19 mg, 0.10 mmol), and diisopropylamine (854 μL, 6.00 mmol) in DMF (5 mL) under N_2-atm. The reaction mixture was heated to 60 °C and compound **4a** (159 mg, 1.20 mmol) in DMF (1 mL) was added dropwise over 1 h. The resulting mixture was stirred at 60 °C for 4 h before evaporation. The product was isolated by flash chromatography on silica gel eluting with EtOAc–hexane (2:1); yield 206 mg (61%, *E*/*Z* ratio: 88:12), 100 mg of the isomeric mixture was purified by flash chromatography silica gel eluting with $CHCl_3$–EtOAc (2:1); yield 79 mg pure (*E*)-isomer, yellow crystals, mp 170–173 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ 9.84 (d, *J* 7.9 Hz, 1H, benzofuran), 8.88 (s, 1H, H-2), 8.59 (s, 1H, H-8), 7.59–7.53 (m, 3H, benzofuran), 7.34–7.27 (m, 5H, Ph), 6.82 (s, 1H, CH=), 5.53 (s, 2H, OCH_2), 5.48 (s, 2H, NCH_2); ^{13}C NMR (150 MHz, DMSO-d_6): δ 166.0 (benzofuran), 153.3 (C-6), 151.5 (C-2), 150.2 (C-4), 144.5 (benzofuran), 144.4 (C-8), 136.7 (Ph), 131.4 (benzofuran), 130.0 (benzofuran), 129.6 (C-5), 128.7 (Ph), 127.86 (benzofuran), 127.85 (benzofuran), 127.8 (Ph), 127.6 (Ph), 121.4 (benzofuran), 94.3 (CH=), 73.7 (OCH_2), 46.3 (NCH_2); ^{15}N NMR (50 MHz, $Me^{13}NO_2$): δ −217.0 (N-9), −137.4 (br, N-3 and N-7), −114.9 (N-1); IR (KBr) ν_{max} 1621 (s), 1578 (s), 1469 (m), 1444 (m), 1401 (m), 1088 (m), 982 (m) cm^{-1}; EIMS *m/z* (rel %): 340 (96, M^+), 240 (100), 91 (71); HRMS (EI) found 340.1327, calcd for $C_{21}H_{16}N_4O$ 340.1324.

4.1.3. 9-Benzyl-6-{[2-({[(1,1-Dimethylethyl)dimethylsilyl]oxy}methyl)phenyl]ethynyl}-9*H*-purine (6). 9-Benzyl-6-iodo-9*H*-purine **1a** (168 mg, 0.500 mmol) was added to a stirred solution of $(PPh_3)_2PdCl_2$ (18 mg, 0.025 mmol), CuI (9 mg, 0.05 mmol), and diisopropylamine (427 μL, 3.00 mmol) in DMF (5 mL) under N_2-atm. The reaction mixture was heated to 60 °C and compound **4b** (148 mg, 0.60 mmol) in DMF (1 mL) was added dropwise over 1.5 h. The resulting mixture was stirred at 60 °C for 22 h before evaporation. The product was isolated by flash chromatography on silica gel eluting with $CHCl_3$–EtOAc (1:1); yield 219 mg (96%), pale brownish oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.97 (s, 1H, H-2), 8.07 (s, 1H, H-8), 7.64–7.61 (m, 3H, Ph), 7.43–7.21 (m, 6H, Ph), 5.44 (s, 2H, OCH_2), 5.12 (s, 2H, NCH_2), 0.94 (s, 9H, *t*-Bu), 0.12 [s, 6H, $Si(CH_3)_2$]; ^{13}C NMR (75 MHz, $CDCl_3$): δ 152.6 (C-2), 151.6 (C-4), 145.0 (C-8), 144.9 (Ph), 142.0 (C-6), 134.9 (C-5), 134.4 (Ph), 132.6 (Ph), 130.1 (Ph), 129.2 (Ph), 128.7 (Ph), 127.8 (Ph), 126.4 (Ph), 125.7 (Ph), 117.9 (Ph), 95.0 (C≡), 88.9 (C≡), 63.2 (OCH_2), 47.4 (NCH_2), 26.0 (CH_3 in *t*-Bu), 18.4 (C in *t*-Bu), −5.3 [$Si(CH_3)_2$]; IR (CCl_4) ν_{max} 3069 (w), 304 (w), 2956 (m), 2930 (m), 2886 (m), 2857 (m), 2213 (m), 1748 (w), 1579 (s) cm^{-1}; CIMS *m/z* (rel %): 455 (76, M+1), 397 (100), 91 (34); HRMS (ESI) found 455.2250, calcd for $C_{27}H_{30}N_4OSi$+H 455.2261.

4.1.4. (*Z*)-9-Benzyl-6-[isobenzofuran-1(3*H*)-ylidenemethyl]-9*H*-purine (7). Method A: The TBS-protected alcohol **6** (200 mg, 0.44 mmol) was dissolved in EtOH (10 mL) and aq HCl (5 mL, 1 M) was added dropwise. The resulting mixture was stirred at ambient temperature for 6 h and quenched by addition of $NaHCO_3$ to neutral pH before evaporation. The product was isolated by flash chromatography on silica gel eluting with EtOAc–EtOH (9:1); yield 99 mg (90%), pale yellow crystals, mp 207–208 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.03 (s, 1H, H-2), 7.94 (s, 1H, H-8), 7.85–7.81 (m, 1H, benzofuran), 7.48–7.26 (m, 8H, Ph and benzofuran), 6.84 (s, 1H, CH=), 5.73 (s, 2H, OCH_2), 5.41 (s, 2H, NCH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.5 (C-2 in benzofuran), 153.3 (C-6), 152.1 (C-2), 150.3 (C-4),

144.2 (C-8), 141.5 (C in benzofuran), 136.8 (C-1 in Ph), 133.4 (C in benzofuran), 130.9 (C in benzofuran), 129.5 (C-5), 128.7 (C in benzofuran), 128.6 (C in benzofuran), 127.9 (C in benzofuran), 127.6 (C in Ph), 120.0 (C in benzofuran), 121.4 (C in benzofuran), 88.0 (CH═), 76.2 (CH_2 in benzofuran), 46.3 (NCH_2); ^{15}N NMR (50 MHz, Me$^{13}NO_2$): δ −217.6 (N-9), −137.3 (br, N-3 and N-7), −109.1 (N-1); IR (KBr) ν_{max} 1635 (s), 1577 (s), 1452 (m), 1398 (m), 1296 (m), 1052 (m), 975 (m) cm^{-1}; EIMS *m/z* (rel %): 340 (97, M$^+$), 249 (100), 91 (34); HRMS (EI) found 340.1321, calcd for $C_{21}H_{16}N_4O$ 340.1324.

Method B: The TBS-protected alcohol **6** (153 mg, 0.34 mmol) was dissolved in THF (5 mL), a solution of tetrabutylammonium fluoride (440 μL, 0.1 mM in THF) was added and the resulting mixture was stirred for 4 h at ambient temperature under N_2-atm. The reaction mixture was evaporated on silica gel and the product was isolated by flash chromatography on silica gel eluting with EtOAc–EtOH (9:1); yield 44 mg (39%); data, see above.

4.1.5. 2-[3-(9-Benzyl-9*H*-purin-6-yl)-2-propynyl]phenol (9a). A mixture of 9-benzyl-6-iodo-9*H*-purine **1a** (169 mg, 0.50 mmol), diisopropylamine (427 μL, 3.00 mmol), $(PPh_3)_2PdCl_2$ (35 mg, 0.05 mmol), and CuI (19 mg, 0.10 mmol) in DMF (5 mL) under N_2-atm was heated to 60 °C. 2-(Prop-2-ynyl)phenol **8** (82 mg, 0.60 mmol) in DMF (1 mL) was added dropwise over 3 h, and the resulting mixture was stirred for 2 h. The product was isolated by flash chromatography on silica gel eluting with EtOAc–EtOH (1:1); yield 50 mg (30%), yellow oil. ^{1}H NMR (300 MHz, CD_3OD): δ 8.96 (s, 1H, H-2), 8.11 (s, 1H, H-8), 7.38–7.24 (m, 6H, Ph), 7.07–6.96 (m, 3H, Ph), 5.44 (s, 2H, CH_2), 5.06 (s, 2H, CH_2); ^{13}C NMR (75 MHz, CD_3OD): δ 157.6 (C-6), 152.7 (C-2), 151.7 (C-4), 145.3 (C-8), 140.8 (Ph), 134.7 (Ph), 134.3 (C-5), 129.5 (Ph), 129.2 (2×C in Ph), 128.7 (Ph), 127.8 (Ph), 121.6 (Ph), 114.9 (2×C in Ph), 93.2 (C≡), 81.4 (C≡), 56.3 (CH_2), 47.4 (NCH_2); IR (neat) ν_{max} 3063 (m), 2987 (m), 1593 (s), 1494 (s), 1403 (s) cm^{-1}; EIMS *m/z* (rel %): 340 (81, M$^+$), 247 (54), 91 (100); HRMS (EI) found 340.1313, calcd for $C_{21}H_{16}N_4O$ 340.1324.

4.1.6. 2-{3-[9-(4-Chlorobenzyl)-9*H*-purin-6-yl]-2-propynyl}phenol (9b). A mixture of 6-chloro-9-[(4-chlorophenyl)methyl]-9*H*-purine **1b** (140 mg, 0.500 mmol), diisopropyl(ethyl)amine (424 μL, 3.00 mmol), $(PPh_3)_2PdCl_2$ (35 mg, 0.05 mmol), and CuI (19 mg, 0.10 mmol) in DMF (5 mL) was heated to 80 °C under N_2-atm. 2-(Prop-2-ynyl)-phenol **8** (82 mg, 0.60 mmol) in DMF (1 mL) was added dropwise over 3 h, and the resulting mixture was stirred for another 3.5 h. The product was isolated by flash chromatography on silica gel eluting with EtOAc–$CHCl_3$ (1:1); yield 50 mg (27%), yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.92 (s, 1H, H-2), 8.07 (s, 1H, H-8), 7.32–7.20 (m, 5H, Ph), 7.03 (m, 3H, Ph), 5.38 (s, 2H, CH_2), 5.03 (s, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.6 (C-6), 152.8 (C-2), 151.6 (C-4), 145.1 (C-8), 141.0 (Ph), 134.8 (Ph), 134.4 (C-5), 133.2 (Ph), 129.5 (Ph), 129.2 (Ph), 121.7 (Ph), 115.0 (Ph), 93.5 (C≡), 81.4 (C≡), 56.4 (CH_2), 46.8 (CH_2); IR (neat) ν_{max} 3420 (br), 3063 (m), 2239 (w), 1897 (w), 1593 (s), 1495 (s), 1437 (s), 1403 (s) cm^{-1}; EIMS *m/z* (rel %): 376/374 (26/87, M$^+$), 249 (100), 125 (96); HRMS (EI) found 374.0946, calcd for $C_{21}H_{15}N_4OCl$ 374.0934.

4.1.7. 2-[3-(9-Tetrahydropyran-2-yl-9*H*-purin-6-yl)-2-propynyl]phenol (9c). A mixture of 6-chloro-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purine **1c** (476 mg, 2.00 mmol), diisopropyl(ethyl)amine (2.08 mL, 12.0 mmol), $(PPh_3)_2PdCl_2$ (140 mg, 0.20 mmol), and CuI (76 mg, 0.40 mmol) in DMF (8 mL) was heated to 60 °C under N_2-atm. 2-(Prop-2-ynyl)phenol **8** (344 mg, 2.40 mmol) in DMF (4 mL) was added dropwise over 5.5 h, and the resulting mixture was stirred for another 0.5 h. The product was isolated by flash chromatography on silica gel eluting with EtOAc–$CHCl_3$ (1:1); yield 294 mg (44%), yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.89 (s, 1H, H-2), 8.31 (s, 1H, H-8), 7.29–7.24 (m, 2H, Ph), 7.02–6.92 (m, 2H, Ph), 5.75 (dd, *J* 9.8 and 2.6 Hz, 1H, H-2 in THP), 5.02 (s, 2H, CH_2), 4.13 (dd, *J* 11.5 and 3.8 Hz, 1H, H-6$_a$ in THP), 3.74 (dt, *J* 11.5 and 2.6 Hz, 1H, H-6$_b$ in THP), 2.09–2.02 (m, 3H, THP), 1.75–1.63 (m, 3H, THP); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.5 (Ph), 152.4 (C-2), 150.7 (C-4), 143.3 (C-8), 140.6 (C-6), 134.5 (C-5), 129.4 (Ph), 121.5 (Ph), 114.8 (Ph), 93.1 (C≡), 82.0 (C-2 in THP), 81.4 (C≡), 68.6 (C-6 in THP), 56.2 (CH_2), 31.6 (THP), 24.7 (THP), 22.6 (THP); IR (neat) ν_{max} 3446 (br), 3102 (m), 3060 (m), 2947 (s), 2859 (s), 2240 (m), 1735 (w), 1583 (s), 1494 (s), 1441 (s), 1403 (s) cm^{-1}; CIMS (CH_4) *m/z* (rel %): 335 (14, M+1), 251 (100); HRMS (CI) found 335.1510, calcd for $C_{19}H_{19}N_4O_2$+H 335.1508.

4.1.8. 2-[3-(2-Chloropyrimidin-4-yl)-2-propynyl]phenol (9d). A mixture of 2,4-dichloropyrimidine (149 mg, 1.00 mmol), diisopropyl(ethyl)amine (1.02 mL, 6.00 mmol), $(PPh_3)_2PdCl_2$ (35 mg, 0.05 mmol), and CuI (19 mg, 0.10 mmol) in DMF (5 mL) was heated to 60 °C under N_2-atm. 2-(Prop-2-ynyl)phenol **8** (163 mg, 1.20 mmol) in DMF (1 mL) was added dropwise over 3 h, and the resulting mixture was stirred for another 2 h. The product was isolated by flash chromatography on silica gel eluting with hexane–EtOAc (4:1); yield 44 mg (18%), brownish oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.53 (d, *J* 5.1 Hz, 1H, H-6), 7.29–7.21 (m, 3H, Ph H-5), 6.99–6.93 (m, 2H, Ph), 4.89 (s, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.2 (C-2), 159.6 (C-6), 157.3 (Ph), 152.3 (C-4), 129.6 (2×C in Ph), 121.9 (Ph), 121.8 (C-5), 114.8 (2×C in Ph), 91.1 (C≡), 83.2 (C≡), 56.0 (CH_2); IR (neat) ν_{max} 3043 (w), 2917 (w), 2237 (w), 1561 (s), 1495 (m) cm^{-1}; EIMS *m/z* (rel %): 246/244 (42/100, M$^+$), 215/217 (71/26), 151 (47); HRMS (EI) found 244.0394, calcd for $C_{13}H_9N_2OCl$ 244.0403.

4.1.9. 2-[3-(Pyridin-2-yl)-2-propynyl]phenol (9e). 2-Bromopyridine (158 mg, 1.00 mmol), $(PPh_3)_2PdCl_2$ (70 mg, 0.10 mmol), CuI (38 mg, 0.20 mmol) diisopropyl(ethyl)-amine (1.04 mL, 6.00 mmol), and 2-(prop-2-ynyl)phenol **6** (163 mg, 1.20 mmol) was reacted as described for **9b** above. The product was isolated by flash chromatography on silica gel eluting with hexane–EtOAc (1:1); yield 123 mg (59%), brownish oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.55 (d, *J* 4.5 Hz, 1H, Ar), 7.60–7.57 (m, 1H, Ar), 7.41–7.38 (m, 1H, Ar), 7.32–7.27 (m, 2H, Ar), 7.24–7.21 (m, 1H, Ar), 7.03–6.95 (m, 2H, Ar), 4.91 (s, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.7 (Ar), 150.0 (Ar), 142.5 (Ar), 136.1 (Ar), 129.5 (Ar), 127.3 (Ar), 123.2 (Ar), 121.5 (Ar), 114.9 (Ar), 86.2 (C≡), 83.9 (C≡), 56.3 (CH_2); IR (CCl_4) ν_{max} 3066

(w), 1599 (m), 1583 (s), 1495 (s) cm^{-1}; EIMS *m/z* (rel %): 209 (74, M^+), 116 (100); HRMS (EI) found 209.0839, calcd for $C_{14}H_{11}NO$ 209.0841; Anal. found: C, 80.16; H, 5.60; N, 7.00. $C_{14}H_{11}NO$ requires C, 80.36; H, 5.30; N, 6.69%.

4.1.10. 2-[3-(*p*-Nitrophenyl)-2-propynyl]phenol (9f). 1-Bromo-4-nitrobenzene (202 mg, 1.00 mmol), $(PPh_3)_2PdCl_2$ (70 mg, 0.10 mmol), CuI (38 mg, 0.20 mmol), diisopropyl-(ethyl)amine (1.04 mL, 6.00 mmol), and 2-(prop-2-ynyl)-phenol **8** (163 mg, 1.20 mmol) was reacted as described for **9b** above. The product was isolated by flash chromatography on silica gel eluting with hexane–EtOAc (95:5); yield 166 mg (66%), mp 83–85 °C, off-white crystals. ^1H NMR (300 MHz, $CDCl_3$): δ 8.17–8.14 (m, 2H, Ph), 7.58–7.54 (m, 2H, Ph), 7.35–7.29 (m, 2H, Ph), 7.03–6.98 (m, 2H, Ph), 4.92 (s, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.5 (Ph), 147.3 (Ph), 132.5 (Ph), 129.5 (Ph), 129.1 (Ph), 123.5 (Ph), 121.7 (Ph), 114.9 (Ph), 89.3 (C≡), 85.1 (C≡), 56.3 (CH_2); IR (KBr) ν_{max} 3415 (br), 3107 (w), 2856 (w), 1592 (s), 1519 (s), 1490 (s) cm^{-1}; EIMS *m/z* (rel %): 253 (63, M^+), 160 (100), 130 (99); HRMS (EI) found 253.0737, calcd for $C_{15}H_{11}NO_3$ 253.0738; Anal. found: C, 71.11; H, 4.38. $C_{15}H_{11}NO_3$ requires C, 71.14; H, 4.38%.

4.1.11. 2-(3-Phenyl-2-propynyl)phenol (9g). Iodobenzene (114 μL, 1.00 mmol), $(PPh_3)_2PdCl_2$ (71 mg, 0.100 mmol), CuI (38 mg, 0.20 mmol), diisopropylamine (0.84 mL, 6.0 mmol), and 2-(prop-2-ynyl)phenol **8** (163 mg, 1.20 mmol) was reacted as described for **9b** above. The product was isolated by flash chromatography on silica gel eluting with hexane–acetone (199:1); yield 169 mg (81%), mp 44–45 °C, pale yellow crystals. ^1H NMR (300 MHz, $CDCl_3$): δ 7.46–7.42 (m, 2H, Ph), 7.34–7.28 (m, 4H, Ph), 7.05–6.97 (m, 3H, Ph), 4.91 (s, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.2 (Ph), 132.2 (Ph), 129.9 (Ph), 129.1 (Ph), 128.7 (Ph), 122.7 (Ph), 121.6 (Ph), 115.4 (Ph), 87.6 (C≡), 84.4 (C≡), 57.1 (CH_2); IR (KBr) ν_{max} 3436 (br), 3050 (w), 2964 (w), 2930 (w), 2196 (w), 1598 (m), 1586 (m), 1489 (s) cm^{-1}; EIMS *m/z* (rel %): 208 (19, M^+), 115 (100); HRMS (EI) found 208.0886, calcd for $C_{15}H_{12}O$ 208.0888; Anal. found: C, 86.30; H, 5.72. $C_{15}H_{12}O$ requires C, 86.51; H, 5.81%.

4.1.12. 9-Benzyl-6-(3-phenoxypropa-1,2-dienyl)-9H-purine (10a). A mixture of 9-benzyl-6-iodo-9*H*-purine **1a** (336 mg, 1.00 mmol), $(PPh_3)_2PdCl_2$ (35 mg, 0.05 mmol), CuI (19 mg, 0.10 mmol), and diisopropylamine (854 μL, 6.00 mmol) in DMF (5 mL) was stirred under N_2-atm at 60 °C, and 2-(prop-2-ynyl)phenol **8** (163 mg, 1.20 mmol) in DMF (1 mL) was added dropwise over 3 h. The mixture was stirred for another 24 h at 60 °C. The product was isolated by flash chromatography on silica gel eluting with EtOAc–hexane (3:2); yield 139 mg (41%), mp 83–85 °C, yellow crystals. ^1H NMR (500 MHz, CD_3OD): δ 8.43 (s, 1H, H-2), 8.04 (s, 1H, H-8), 7.32–7.28 (m, 7H, Ph), 7.08–7.00 (m, 1H, Ph), 6.99–6.98 (m, 2H, Ph), 6.59 (d, *J* 3.9 Hz, 1H, =CH), 6.33 (d, *J* 3.9 Hz, 1H, =CH), 5.41 (s, 2H, NCH_2); ^{13}C NMR (125 MHz, CD_3OD): δ 159.1 (Ph), 140.0 (C-8), 137.9 (Ph), 135.6 (Ph), 134.6 (C-4), 133.6 (C-2), 131.1 (Ph), 129.9 (Ph), 129.1 (Ph and =C=), 128.8 (Ph), 125.5 (Ph), 124.8 (C-5), 123.4 (C-6), 116.9 (Ph), 101.4 (CH= in allene), 94.1 (CH= in allene), 49.0 (NCH_2); IR (neat) ν_{max} 3108 (w), 2943 (w), 1639 (m), 1556 (s), 1490 (s) cm^{-1}; EIMS *m/z* (rel %): 340 (88, M^+), 263 (42), 91 (100); HRMS (EI) found 340.1320, calcd for $C_{21}H_{16}N_4O$ 340.1324.

4.1.13. 9-(4-Chlorobenzyl)-6-(3-phenoxypropa-1,2-dienyl)-9*H*-purine (10b). A mixture of compound **9b** (50 mg, 0.14 mmol) and CuI (3 mg, 0.014 mmol) in Et_3N (5 mL) was refluxed under N_2-atm for 24 h. The product was isolated by flash chromatography on silica gel eluting with EtOAc–hexane (2:1); yield 10 mg (20%), brownish oil. ^1H NMR (600 MHz, CD_3OD): δ 8.40 (s, 1H, H-2), 7.73 (s, 1H, H-8), 7.32–7.27 (m, 4H, Ph), 7.20 (m, 2H, Ph), 7.10 (m, 1H, Ph), 7.00 (m, 2H, Ph), 6.65 (dd, *J* 3.9 and 0.7 Hz, 1H, =CH), 6.35 (d, *J* 3.9 Hz, 1H, =CH), 5.41 (s, 2H, NCH_2); ^{13}C NMR (150 MHz, CD_3OD): δ 157.7 (Ph), 137.9 (C-8), 134.5 (Ph), 133.8 (Ph), 133.6 (C-4), 134.2 (=C=), 132.2 (C-2), 129.9 (Ph), 129.3 (Ph), 128.2 (Ph), 125.3 (C-5), 123.7 (Ph), 122.8 (C-6), 115.8 (Ph), 100.7 (=CH in allene), 93.1 (=CH in allene), 46.9 (NCH_2); EIMS *m/z* (rel %): 376/374 (37/100, M^+), 299/297 (15/45), 127/125 (21/65); HRMS (EI) found 374.0930, calcd for $C_{21}H_{15}N_4OCl$ 374.0934.

4.1.14. 6-(3-Phenoxypropa-1,2-dienyl)-9-(tetrahydropyran-2-yl)-9*H*-purine (10c). A mixture of compound **9c** (140 mg, 0.42 mmol) and CuI (8 mg, 0.042 mmol) in Et_3N (5 mL) was refluxed under N_2-atm for 16 h. The product was isolated by flash chromatography on silica gel eluting with EtOAc–EtOH (99:1); yield 54 mg (39%), yellow oil. ^1H NMR (500 MHz, $CDCl_3$): δ 8.39 (s, 1H, H-2), 7.96 (s, 1H, H-8), 7.31–7.28 (m, 2H, Ph), 7.09–7.06 (m, 1H, Ph), 6.99–6.97 (m, 2H, Ph), 6.64 (dd, *J* 3.9 and 0.8 Hz, 1H, CH=), 6.35 (d, *J* 3.9 Hz, 1H, CH=), 5.68–5.66 (m, 1H, H-2 in THP), 4.15 (dd, *J* 11.7 and 2.3 Hz, 1H, H-6_a in THP), 3.74 (dt, *J* 11.7 and 2.3 Hz, 1H, H-6_b in THP), 2.11–2.02 (m, 3H, THP), 1.76–1.62 (m, 3H, THP); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.7 (Ph), 136.2 (C-8), 133.6 (=C=), 132.6 (C-2), 132.0 (C-4), 129.9 (Ph), 125.1 (C-5), 122.0 (C-6), 123.6 (Ph), 115.7 (Ph), 100.8 (=CH in allene), 93.1 (=CH in allene), 82.1 (C-2 in THP), 68.7 (THP), 31.7 (THP), 24.9 (THP), 22.9 (THP); IR (neat) ν_{max} 2947 (m), 2858 (m), 1641 (m), 1579 (m), 1552 (s), 1490 (s) cm^{-1}; EIMS *m/z* (rel %): 334 (24, M^+), 250 (100), 173 (89); HRMS (EI) found 334.1432, calcd for $C_{19}H_{19}N_4O_2$ 334.1430.

4.1.15. 2-Chloro-4-(3-phenoxypropa-1,2-dienyl)-pyrimidine (10d). A mixture of compound **9d** (44 mg, 0.18 mmol) and CuI (4 mg, 0.018 mmol) in Et_3N (5 mL) was refluxed under N_2-atm for 26 h. The compound was isolated by flash chromatography on a silica gel eluting with hexane–EtOAc (4:1); yield 17 mg, (39%), pale yellow oil. ^1H NMR (500 MHz, CD_3OD): δ 8.56 (d, *J* 1.3 Hz, 1H, H-6), 7.37–7.34 (m, 3H, H-5 and 2H in Ph), 7.15–7.12 (m, 1H, Ph), 7.04–7.02 (m, 2H, Ph), 6.43 (s, 2H, 2×CH= in allene); ^{13}C NMR (125 MHz, CD_3OD): δ 158.6 (Ph), 136.1 (C-6), 135.2 (=C=), 134.5 (C-2), 131.2 (Ph), 127.2 (C-4), 125.2 (Ph), 117.2 (Ph), 113.0 (C-5), 103.8 (CH= in allene), 98.7 (CH= in allene); EIMS *m/z* (rel %): 246/244 (25/72, M^+), 169/167 (36/100); HRMS (EI) found 244.0402, calcd for $C_{13}H_9N_2OCl$ 244.0403.

4.1.16. 9-Benzyl-6-(3-phenoxy-1-propynyl)-9*H*-purine (12a). A mixture of 9-benzyl-6-iodo-9*H*-purine **1a** (336 mg,

1.00 mmol), $(PPh_3)_2PdCl_2$ (35 mg, 0.05 mmol), CuI (19 mg, 0.10 mmol), and diisopropylamine (854 μL, 6.00 mmol) in DMF (5 mL) was heated to 60 °C. Phenyl propargyl ether (154 μL, 1.20 mmol) in DMF (1 mL) was added dropwise over 2 h, and the resulting mixture was stirred for 7 h. The product was isolated by flash chromatography on silica gel eluting with EtOAc–hexane (3:1); yield 145 mg (43%) as a 13:87 mixture of **12a** and **10a**, NMR data for **12a**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.93 (s, 1H, H-2), 8.06 (s, 1H, H-8), 7.33–7.00 (m, 10H, Ph), 5.47 (s, 2H, NCH_2), 5.03 (s, 2H, OCH_2).

4.1.17. 9 Benzyl-6-(4-phenyl-1-butynyl)-9*H*-purine (12b). A mixture of 9-benzyl-6-iodo-9*H*-purine **1a** (336 mg, 1.00 mmol), $(PPh_3)_2PdCl_2$ (35 mg, 0.05 mmol), CuI (19 mg, 0.10 mmol), and diisopropyl(ethyl)amine (1.02 mL, 6.00 mmol) in DMF (5 mL) was heated to 60 °C under N_2-atm. 4-Phenyl-1-butyne (169 μL, 1.20 mmol) in DMF (1 mL) was added dropwise over 2 h, and the resulting mixture was stirred for 4 h. The product was isolated by flash chromatography on silica gel eluting with hexane–EtOAc (1:1); yield 289 (86%), pale brownish oil. ^{1}H NMR (300 MHz, CD_3OD): δ 8.81 (s, 1H, H-2), 8.55 (s, 1H, H-8), 7.35–7.15 (m, 10H, Ph), 5.50 (s, 2H, NCH_2), 3.02–2.98 (m, 2H, CH_2), 2.90–2.84 (m, 2H, CH_2); ^{13}C NMR (75 MHz, CD_3OD): δ 153.3 (C-2), 152.8 (C-4), 148.2 (C-8), 142.6 (Ph), 141.6 (C-6), 137.0 (Ph), 135.1 (C-5), 130.0 (Ph), 129.5 (Ph), 129.4 (Ph), 129.0 (Ph), 127.5 (Ph), 102.5 (C≡), 76.9 (C≡), 48.3 (NCH_2), 35.3 (CH_2), 22.7 (CH_2), one C in Ph was hidden; IR (neat) ν_{max} 3088 (m), 2930 (m), 2862 (m), 2233 (s), 1734 (w), 1710 (w), 1582 (s), 1497 (s) cm^{-1}; EIMS *m/z* (rel %): 338 (72, M^+), 247 (51), 91 (100); HRMS (EI) found 338.1529, calcd for $C_{22}H_{18}N_4$ 338.1531.

4.1.18. 2-Chloro-4-(3-phenoxy-1-propynyl)pyrimidine (12c). A mixture of 2,4-dichloropyrimidine (149 mg, 1.00 mmol), $(PPh_3)_2PdCl_2$ (35 mg, 0.05 mmol), CuI (19 mg, 0.10 mmol), and diisopropyl(ethyl)amine (1.02 mL, 6.00 mmol) in DMF (5 mL) was heated to 60 °C under N_2-atm. Phenyl propargyl ether (158 μL, 1.20 mmol) in DMF (1 mL) was added dropwise over 2 h, and the resulting mixture was stirred for 3 h. The product was isolated by flash chromatography on silica gel eluting with hexane–EtOAc (4:1); yield 74 mg (30%), brownish oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.57 (d, *J* 5.0 Hz, 1H, H-6), 7.33 (m, 3H, Ph and H-5), 7.03–6.96 (m, 3H, Ph), 4.92 (s, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.6 (C-2), 159.6 (C-6), 157.4 (C in Ph), 152.3 (C-4), 129.6 (CH in Ph), 122.0 (C-5), 121.8 (CH in Ph), 114.8 (CH in Ph), 91.1 (C≡), 83.2 (C≡), 56.0 (CH_2); IR (CCl_4) ν_{max} 3043 (w), 2959 (w), 2926 (w), 2860 (w), 2237 (w), 1599 (s), 1590 (s), 1495 (s) cm^{-1}; EIMS *m/z* (rel %): 246/244 (33/100, M^+), 151 (11); HRMS (EI) found 244.0402, calcd for $C_{13}H_9N_2OCl$ 244.0403.

4.1.19. 2-(3-Phenoxy-1-propynyl)pyridine (12d). A mixture of 2-bromopyridine (96 μL, 1.0 mmol), $(PPh_3)_2PdCl_2$ (35 mg, 0.05 mmol), CuI (19 mg, 0.10 mmol), and diisopropyl(ethyl)amine (1.02 mL, 6.00 mmol) in DMF (5 mL) was heated to 60 °C under N_2-atm. Phenyl propargyl ether (158 μL, 1.20 mmol) in DMF (1 mL) was added dropwise over 3 h, and the resulting mixture was stirred for another 3 h. The product was isolated by flash chromatography on silica gel eluting with hexane–EtOAc (2:1), yield 79 mg (38%), brownish oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.55 (d, *J* 4.4 Hz, 1H, H-6), 7.61–7.58 (m, 1H, H-3), 7.41–7.39 (m, 1H, H-4), 7.32–7.27 (m, 2H, Ph), 7.24–7.22 (m, 1H, H-5), 7.03–6.95 (m, 3H, Ph), 4.92 (s, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.7 (C in Ph), 150.6 (C-6), 142.5 (C-2), 136.1 (C-3), 129.5 (CH in Ph), 127.3 (C-4), 123.2 (C-5), 121.5 (CH in Ph), 114.9 (CH in Ph), 86.2 (C≡), 84.0 (C≡), 56.3 (CH_2); IR (CCl_4) ν_{max} 3065 (w), 2918 (w), 2862 (w), 1599 (s), 1583 (s), 1495 (s), 1464 (s) cm^{-1}; EIMS *m/z* (rel %): 209 (96, M^+), 116 (100); HRMS (EI) found 209.0831, calcd for $C_{14}H_{11}NO$ 209.0841; Anal. Found: C, 80.35; H, 5.41; N, 6.62. $C_{14}H_{11}NO$ requires C, 80.36; H, 5.30; N 6.69%.

4.1.20. 1-Nitro-4-(3-phenoxy-1-propynyl)benzene (12e). A mixture of 1-bromo-4-nitrobenzene (202 mg, 1.00 mmol), $(PPh_3)_2PdCl_2$ (35 mg, 0.05 mmol), CuI (19 mg, 0.10 mmol), and diisopropyl(ethyl)amine (1.02 mL, 6.00 mmol) in DMF (5 mL) was heated to 60 °C under N_2-atm. Phenyl propargyl ether (158 μL, 1.20 mmol) in DMF (1 mL) was added dropwise over 2.5 h, and the resulting mixture was stirred for 2.5 h. The product was isolated by flash chromatography on silica gel eluting with hexane–EtOAc (9:1); yield 175 mg (69%), off-white crystals, mp 87–89 °C (lit.[31] 76–77 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.18–8.14 (m, 2H, Ph), 7.57–7.54 (m, 2H, Ph), 7.34–7.24 (m, 2H, Ph), 7.02–6.98 (m, 3H, Ph), 4.93 (s, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.0 (C in Ph), 147.8 (C in Ph), 133.0 (CH in Ph), 130.0 (CH in Ph), 129.5 (C in Ph), 124.0 (CH in Ph), 122.2 (CH in Ph), 115.3 (CH in Ph), 89.7 (C≡), 85.6 (C≡), 56.8 (CH_2); EIMS *m/z* (rel %): 253 (97, M^+), 160 (100); HRMS (EI) found 253.0733, calcd for $C_{15}H_{11}NO_3$ 253.0738.

4.1.21. (3-Phenoxy-1-propynyl)benzene (12f). A mixture of iodobenzene (112 μL, 1.00 mmol), $(PPh_3)_2PdCl_2$ (35 mg, 0.05 mmol), CuI (19 mg, 0.10 mmol), and diisopropyl(ethyl)amine (1.02 mL, 6.00 mmol) in DMF (5 mL) was heated to 60 °C under N_2-atm. Phenyl propargyl ether (158 μL, 1.20 mmol) in DMF (1 mL) was added dropwise over 2 h, and the resulting mixture was stirred for 3 h. The product was isolated by flash chromatography on silica gel eluting with hexane–EtOAc (9:1); yield 208 mg (quant.), off-white crystals, mp 44–45 °C (lit.[31] 44 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44–7.41 (m, 2H, Ph), 7.33–7.24 (m, 5H, Ph), 7.04–6.96 (m, 3H, Ph), 4.91 (CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.8 (Ph), 131.8 (Ph), 129.5 (Ph), 128.6 (Ph), 128.3 (Ph), 122.3 (Ph), 121.4 (Ph), 115.0 (Ph), 87.1 (C≡), 83.9 (C≡), 56.6 (CH_2); EIMS *m/z* (rel %): 208 (40, M^+), 115 (100); HRMS (EI) found 208.0885, calcd for $C_{15}H_{12}O$ 208.0888.

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