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Full Paper

Full Cleavage of C≡C Bond in Electron-Deficient Alkynes via Reaction with Ethylenediamine

Sergei F. Vasilevsky,[A,D] *Maria P. Davydova,*[A] *Victor I. Mamatyuk,*[B] *Nikolay Tsvetkov,*[C] *Audrey Hughes,*[C] *Denis S. Baranov,*[A] *and Igor V. Alabugin*[C,D]

[A]Voevodsky Institute of Chemical Kinetics and Combustion, Siberian Branch of the Russian Academy of Science, 3 Institutskaya Street, Novosibirsk 630090, Russia.
[B]Vorozhtsov Novosibirsk Institute of Organic Chemistry, Siberian Branch of the Russian Academy of Science, Novosibirsk 630090, Russia.
[C]Department of Chemistry and Biochemistry, Florida State University, Tallahassee, FL 32306, USA.
[D]Corresponding authors. Email: vasilev@kinetics.nsc.ru; alabugin@chem.fsu.edu

Reaction of 1,2-diaminioethane (ethylenediamine) with electron-deficient alkynes leads to full scission of the C≡C bond even in the absence of a keto group directly attached to the alkyne. This process involves oxidation of one of the alkyne carbons into C2 of a 2-*R*-4,5-dihydroimidazole with the concomitant reduction of the other carbon to a methyl group. The sequence of Sonogashira coupling with the ethylenediamine-mediated fragmentation described in this work can be used for selective formal substitution of halogen in aryl halides by a methyl group or a 4,5-dihydroimidazol-2-yl moiety.

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Introduction

Alkynes are indispensable building blocks for the preparation of conjugated molecules and carbon-rich materials. The unique combination of electronic and spatial features of the triple bond renders the alkyne moiety a useful departure point in the design of new chemical transformations.[1] The electrophilic reactivity of alkynes can be amplified by the presence of electron acceptors conjugated with the triple bond. Such compounds readily undergo addition reactions with nucleophiles, including a variety of cyclization reactions mediated by the formation of new C–C and C–heteroatom bonds.[2]

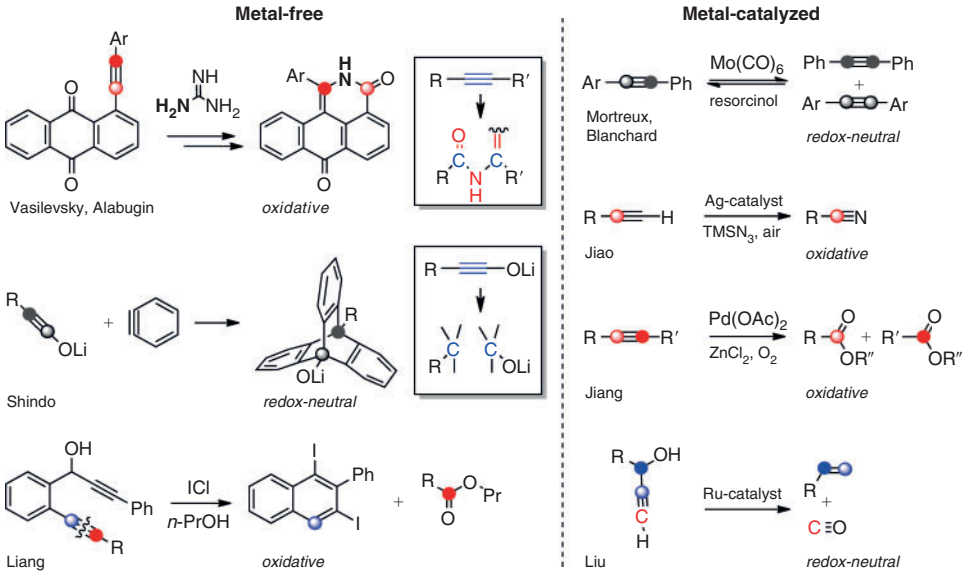
Fragmentation reactions continue to play an important role in the construction of new molecular targets.[3,4] In this context, the fragmentations of carbon–carbon bonds often provide particularly elegant and conceptually unique synthetic disconnections. Such fragmentations can be mediated by metals,[5] or proceed in a metal-free fashion (Scheme 1).[6,7] Furthermore, fragmentations can be further separated into oxidative or redox-neutral processes. For the latter type, the transformation often proceeds via internal disproportionation where one of the carbons at the breaking bond is oxidized whereas the other one is reduced.

We described earlier the complete scission of the triple bond of α-acetylenyl ketones induced by ethylenediamine with the formation of the respective methyl aryl ketones and 2-*R*-imidazolines (Scheme 2).[8] This reactivity pattern contrasts drastically with reports of the (formally) single C(O)–alkyne bond scission in reactions with other nucleophiles. Nenajdenko and coworkers illustrated that this transformation is applicable to strongly polarized CF_3-substituted alkynes generated in situ from the related alkenes.[9] Subsequently, Cheng and coworkers applied this reaction to the preparation of 4(3*H*)-quinazolinones.[10] The latter transformation expands the utility of acceptor alkyne reactants as a one-carbon electrophilic building block in the preparation of 1,3-diaza-containing heterocycles.

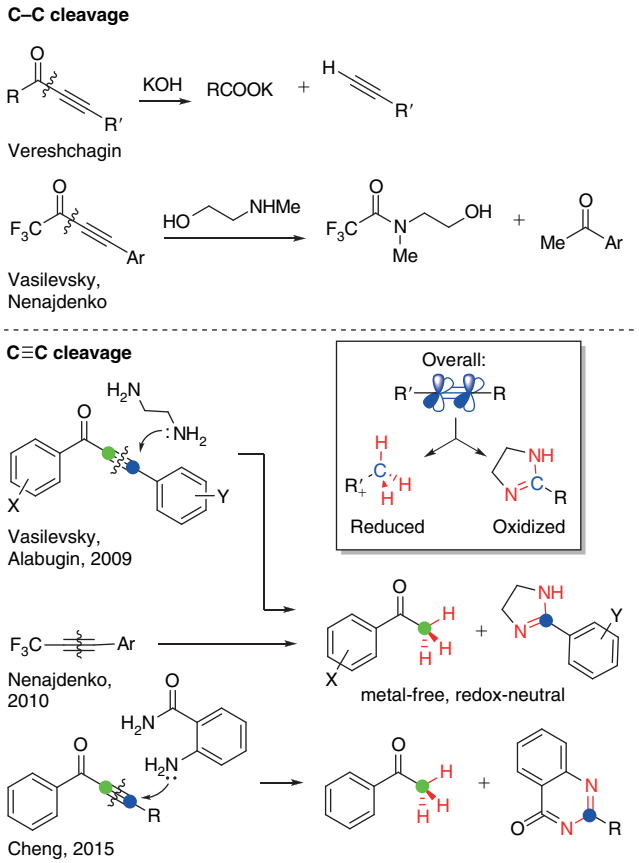
Computational analysis of that fragmentation cascade in ketoalkynes revealed interesting mechanistic features (Scheme 3).[8a] For example, whereas the intermolecular Michael addition was fast, the intramolecular 5-exo-trig closure of the second amino group at the alkene was slow and thermodynamically unfavourable. The presence of the carbonyl group at the alkyne was essential in partially alleviating this thermodynamic penalty by avoiding charge separation at the transition state (TS) where the developing negative charge at the carbonyl could serve as an acceptor for the proton from the NH_2 moiety. Furthermore, the carbonyl group is important for the final C–C scission step where, again, it plays a key part in the six-membered TS that avoids charge separation and makes this step concerted.

The final step of the fragmentation cascade corresponds to a retro-Mannich reaction. It illustrates the inherent connection between the chemistries of alkynes and carbonyl compounds. Because alkynes have the same oxidation level as carbonyl compounds, one can engineer new alkyne cascade transformations by unmasking the hidden 'carbonyl nature' of alkynes.[11]

However, when building bridges between alkynes and carbonyls, one has to remember that alkynes are generally less electrophilic than carbonyls – an expected difference that stems



Scheme 1. Selected examples of alkyne fragmentations. The colour code illustrates the redox features of these processes (red, an oxidized carbon; blue, a reduced carbon; grey, no change in the formal oxidation state).



Scheme 2. Metal-free C–C fragmentations in ketoalkynes and related molecules promoted by bifunctional nucleophiles.

from the inherently lower polarity of the hydrocarbon functionality. In the present work, we investigate the reactivity of a broader selection of polarized alkynes towards ethylenediamine. Our goal is to explore the limits of this remarkable transformation by expanding it to systems where the above assistance from the carbonyl group is unavailable.

Results and Discussion

In the first stage, we concentrated on 1- and 2-phenylethynyl-9,10-anthraquinones (**1a**, **b**). In these vinylogs of α-ketoalkynes, the carbonyl group is removed further away from the triple bond. Variation of solvents, reagent ratios, and temperatures revealed that the fragmentation proceeds most effectively in refluxing pyridine with a 50-fold excess of the nucleophile (Scheme 4).

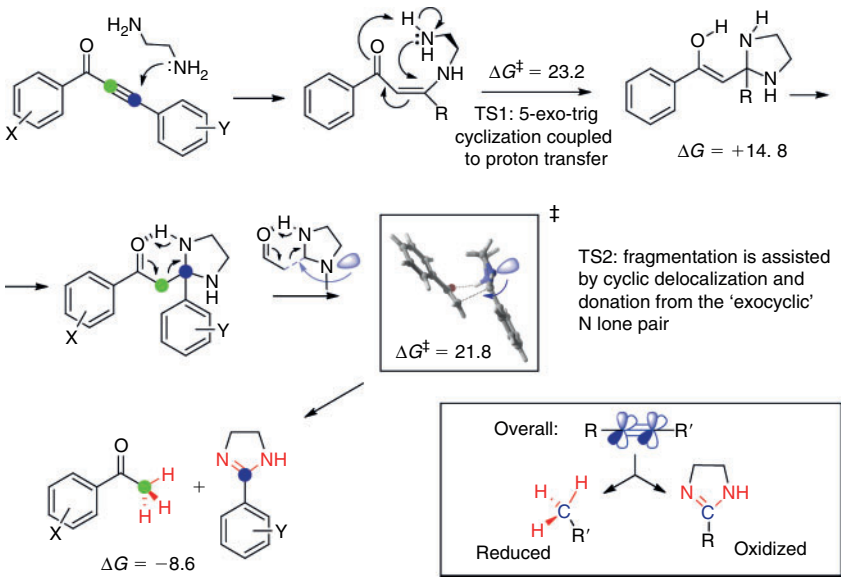
The fragmentation of 1-phenylethynyl-9,10-antraquinone (**1a**) was complete after 3 h. Chromatographic purification of the reaction products led to the isolation of the two alkyne scission products – 1-methyl-9,10-anthraquinone (**2a**, 69 %) and 2-phenyl-4,5-dihydroimidazol (**3a**, 68 %) (Scheme 5).

In addition, we isolated the 6-endo-*dig* cyclization product 2-phenyl-7*H*-dibenzo[*de,h*]quinolin-7-one (**4**) in a yield of 12 %. The formation of the latter product can be described analogously to the earlier published cyclizations of 1-phenylethynyl-9,10-anthraquinones with *N*-polynucleophiles (hydrazine, guanidine, urea, thiourea), leading to 2-*R*-7*H*-dibenzo[*de,h*]quinolin-7-ones (Scheme 6).[12] It is possible that anchimeric assistance[13] (via a homoanomeric[14] interaction with the lone pair of the remote nitrogen atom, as shown with the dashed arrow) is involved in the C–N scission step.

In the next step, we investigated the reactivity of 2-phenylethynyl-9,10-anthraquinone (**1b**), an isomeric substrate where both carbonyl groups are located away from the alkyne but conjugation is maintained via the π-system (Scheme 7). Although the reaction occurs more slowly (5 h), it still leads to full triple-bond scission with the formation of 2-methyl-9,10-anthraquinone (**2b**, 94 %) and 2-phenylimidazoline (**3a**, 93 %) (Scheme 4). Because the C=O and C≡C functional groups are not in the *peri*-arrangement, the 2-phenyl-7H-dibenzo[*de,h*]-quinolin-7-one side product is not formed.

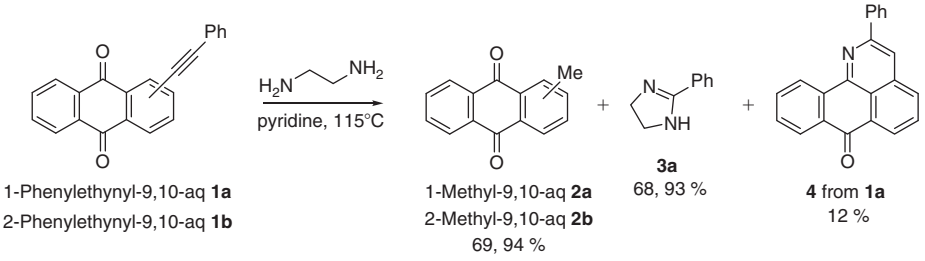
Next, we explored the possibility of expanding the alkyne fragmentation reactions to compounds with other functional groups also positioned away from the alkyne moiety by focussing on the family of nitro-substituted diaryl alkynes with different positions of the acceptor NO_2 group (Scheme 8).

The presence of a single *para*-nitro group in substrate **5a** renders it quite reactive. This compound undergoes triple-bond

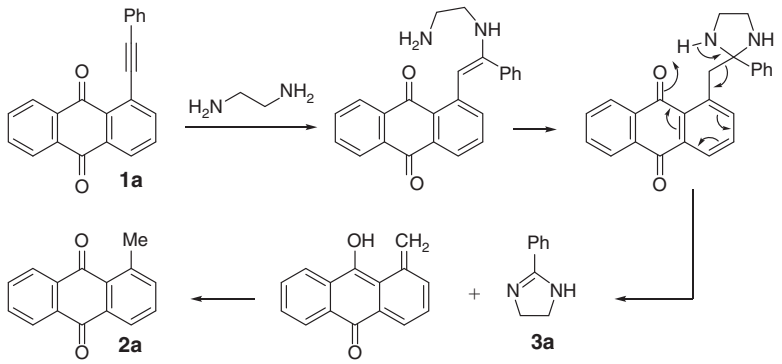


Energies in kcal mol^{-1} at B3LYP/6-31+G(d,p) level with SCRF (THF)

Scheme 3. The sequence of steps in the alkyne fragmentation in the reaction of ketoalkynes and ethylenediamine (1 kcal mol^{-1} = 4.186 kJ mol^{-1}).



Scheme 4. Fragmentation of phenylethynyl-9,10-anthraquinones **1a**, **b**. aq = anthraquinone.

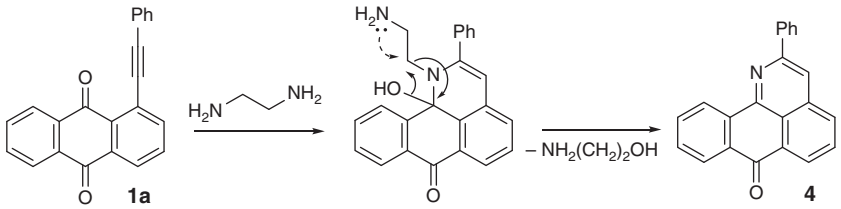


Scheme 5. Possible mechanism of fragmentation of **1a**.

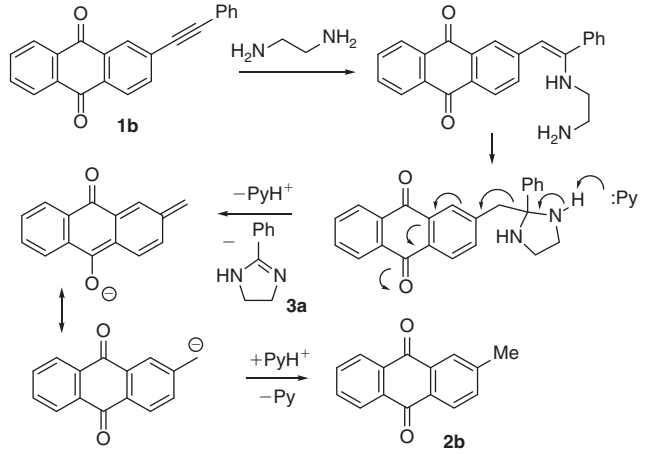
scission in the reaction with 1,2-diaminoethane after 3 h, yielding the expected fragmentation products, 1-methyl-4-nitrobenzene (**6a**, 68 %) and 2-phenylimidazoline (**3a**, 61 %).

The introduction of two donor methyl groups into the nitro-substituted aromatic ring led, as expected, to a slower reaction (6 h). However, the nature of the products did not change and both 1,2,4-trimethyl-5-nitrobenzene (**6b**) and imidazoline **3a** were formed in high yields (87 and 81 % respectively).

However, the fragmentation is not observed for substrates **5c** and **5d** where the nitro group does not electronically communicate with the alkyne. For the *meta*-nitro-substituted substrate **5c**, the starting material was recovered in 80 % yield after 40 h of reflux. For compound **5d**, the combined activating effects of the nitro and alkyne groups activate the OMe moiety towards nucleophilic substitution, with the formation of the substitution product **8** (Scheme 8).



Scheme 6. Possible route of formation of 2-phenyl-7*H*-dibenzo[d*e*,*h*]quinolin-7-one (**4**).



Scheme 7. Possible route of fragmentation of **1b**.

However, the 'push–pull' alkyne **5e**, where the NO_2 acceptor and the OMe donor are positioned at the *para*-positions of the two rings at the opposite alkyne termini, does undergo the full fragmentation. Although the lowered electron deficiency of the alkyne leads to longer reaction time (8 h is needed to reach full conversion), the isolated yields of 1-methyl-4-nitrobenzene (**6a**) and 2-(4-methoxyphenyl)-imidazoline (**3b**) were 62 and 66 % respectively.

The electron-deficiency of the alkyne moiety is more important than alkyne polarization. For example, 1,2-bis(4-nitrophenyl) ethyne (**5f**), a symmetric alkyne with two acceptor groups, reacts faster (1 h), yielding 51 % 1-methyl-4-nitrobenzene (**6a**) and 55 % imidazoline **3c**.

As expected, a polarized but electron-rich alkyne 1-methoxy-4-(phenylethynyl)benzene (**5g**), containing a donor OCH_3 group, was unreactive. In this case, the starting material was recovered in 85 % yield after 50 h.

We also explored the possibility of expanding this chemistry to polarized heterocycles. Considering the acceptor nature of the pyridine moiety, it was interesting to test whether the pyridine group can mimic the activating effect of the nitro group on the triple bond.

Under analogous conditions (refluxing pyridine in a closed vial at 120°C), the reaction of 4-phenylethynyl pyridine (**7a**) is significantly slower. After 6 h, the fragmentation is incomplete – NMR analysis of the reaction mixture revealed the intermediate Michael addition product, 4-methylpyridine (picoline, **9**) and 2-phenyl-4,5-dihydroimidazole (**3a**) in a 1.4 : 1 : 1 ratio. It took additional 14 h under the same conditions to complete the full transformation and produce a 70 % mixture with a 1 : 1 ratio of the two fragmentation products according to the NMR analysis (Scheme 9). We did not attempt to isolate the methylpyridine **9** owing to its volatility. We also tested the possibility of inducing this fragmentation in the absence of pyridine solvent by simply using 10 equiv. of neat ethylenediamine and found that 76 % of the two fragmentation products were formed after 20 h at 120°C in the expected 1 : 1 ratio.

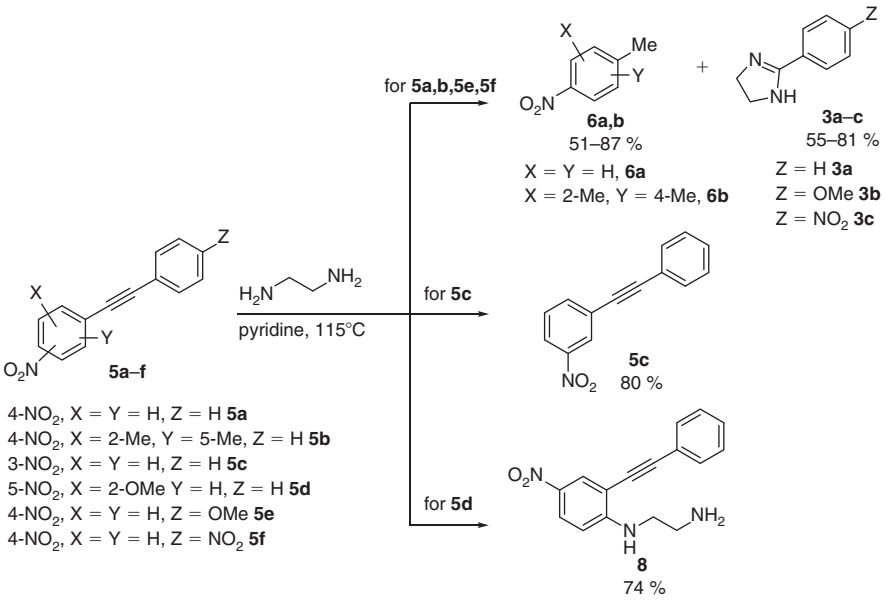
The transformation of 2-phenylethynyl pyridine (**7b**) proceeds in a drastically different manner. Even after 40 h of reflux in pyridine, no fragmentation products were detected. According to NMR analysis, reaction of ethylenediamine with the diaryl alkyne **7b** leads to the formation of 33 % of the enamine **10** (Scheme 10) along with unidentified products. The enamine can be hydrolyzed to give 1-phenyl-2-(pyridin-2-yl)ethanone (**11**), which was identified as the 2,4-dinitrophenylhydrazone (see experimental section).

Computational Analysis

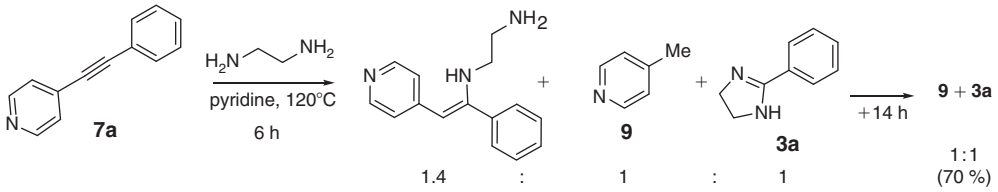
We wanted to gain additional insights into the origin of the observed trends in reactivity by calculating alkyne polarization for the key diaryl alkynes discussed above. We also included the parent diphenyl alkyne, tolane, for comparison. At this stage, we limited ourselves to the analysis of the starting materials instead of the full reaction potential energy profiles. However, even this simple analysis still provided valuable quantitative information regarding the acceptor ability of the different aryl groups (Table 1). The natural bond orbital (NBO) charge on the alkyne carbons of tolane is close to zero (0.006 e). The short strong π-bonds of the alkyne moiety are not easily polarized but introduction of a *p*-nitro group at one of the alkyne carbons increases the positive charge by a factor of 10 (to 0.060 e). The electron-withdrawing effect of a *p*-nitrophenyl group is comparable with that of the 4-pyridine moiety. The effect of anthracene-9,10-dione and the *m*-nitrophenyl group are intermediate whereas the 2-pyridinyl substituent is the least withdrawing of all the aryls investigated in the present work.

The table also includes occupancies and polarizations of the alkyne π-bonds quantified by NBO analysis. The alkyne π-bond conjugated to the acceptor moieties is noticeably depleted of electron density (1.87–1.85 electrons) in comparison with the other π-bond, which is twisted out of the conjugation. However, polarizations of the two π-bonds are generally identical, and π-electron density is increased at the carbon adjacent to the acceptor moiety. The only exception is 2-(phenylethynyl)pyridine, where polarizations of the two π-bonds were found to be opposite, most likely due to the through-space donation from the lone pair of pyridine nitrogen to the in-plane π-system.[15]

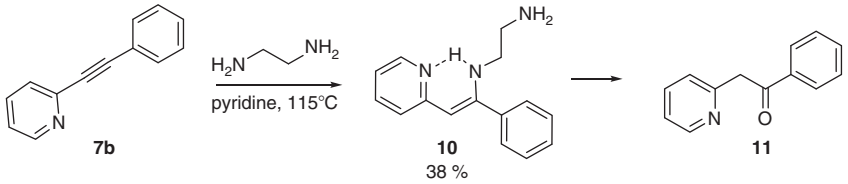
In summary, we have shown that reaction of electron-deficient alkynes with ethylenediamine is a general transformation that can involve not only α-acetylenic ketones but other suitably activated alkynes. From a preparative perspective, the combination of Sonogashira cross-coupling and fragmentation presented in this work opens the door for two, albeit non-atom-economical, but potentially useful synthetic transformations: introduction of methyl groups to electron-deficient aryl halides or triflates or



Scheme 8. Fragmentation of nitro-substituted diaryl acetylenes **5a**–**f**.



Scheme 9. Fragmentation of diaryl acetylene **7a**.



Scheme 10. Reaction of 2-(phenylethynyl)pyridine (**7b**) with 1,2-diaminoethane.

introduction of masked carboxyl (imidazoline) groups into neutral or donor aryl halides or triflates (Scheme 11). These approaches suggest the retrosynthetic equivalency of alkynes and one-carbon synthons in the most reduced and oxidized forms of the latter.

Experimental

Melting points were determined with a Kofler apparatus. Combustion analysis was performed with a CHN- Carlo Erba Model 1106 analyser. IR spectra were recorded in KBr pellets on a Vector 22 instrument. NMR spectra were recorded on Bruker AV-400 spectrometer at 400.13 (^{1}H) and 100.61 MHz (^{13}C) in $CDCl_3$. Column chromatography was performed on SiO_2 (Merck 60 (0.063–0.2 mm)). Analytical TLC was performed with Merck silica gel 60 F_{254} plates. Ethane-1,2-diamine, $PdCl_2(PPh_3)_2$, CuI, and Et_3N were commercially available reactants.

All calculations were performed using the software package *Gaussian '09*.[16] Structures were optimized using the B3LYP/6–31+G(d,p) level of theory, and evaluated using *NBO 3.0*.[17]

*General Procedure: Synthesis of Alkynes **1a–b, 5a–g, 7a–b***

A mixture of the appropriate iodide (bromide) (4.5 mmol), alkyne (4.5 mmol), $PdCl_2(PPh_3)_2$ (0.014 mmol), CuI (0.026 mmol), and Et_3N (19.3 mmol) in benzene was stirred under an argon atmosphere at 65°C for 2–10 h.[18] The volatiles were evaporated under vacuum and the residues were purified on silica (hexane/toluene) to give **1a**–**b**, **5a**–**g**, **7a**–**b**.

*1-(Phenylethynyl)-9,10-anthraquinone (**1a**)*

Yield 89 %, mp 158–160°C (lit. 159–160°C[19]).

*2-(Phenylethynyl)-9,10-anthraquinone (**1b**)*

Yield 93 %, mp 213–214°C (lit. 214.5–215.5°C[20]).

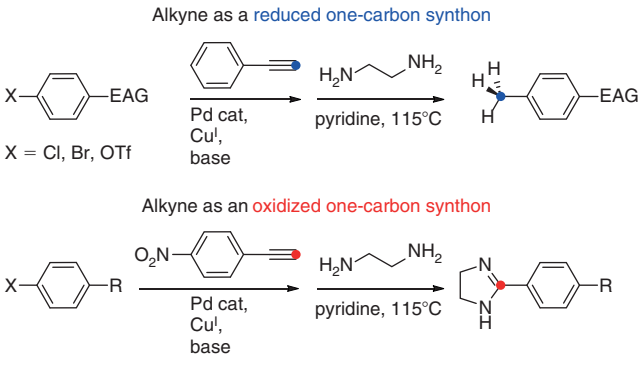
*1-Nitro-4-(phenylethynyl)benzene (**5a**)*

Yield 80 %, mp 120–122°C (lit. 118–120°C[21]).

Table 1. Natural bond order (NBO) analysis of diaryl alkyne polarization at B3LYP/6–31+G(d,p) level of theory

Alkyne	Occupancy	Polarization coefficients[A]	c_A^{2} [B]	Charge
1,2-Diphenylethyne	1.97	C1, π (Ph)	50.00 %	0.006
		C2, π (Ph)	50.00 %	0.006
	1.87	C1, π (Ph)	50.00 %	
		C2, π (Ph)	50.00 %	
1-Nitro-4-(phenylethynyl)benzene (**5a**)	1.97	C1, π (*p*NO_2Ph)	50.24 %	−0.022
		C2, π (Ph)	49.76 %	0.060
	1.85	C1, π (*p*NO_2Ph)	51.34 %	
		C2, π (Ph)	48.66 %	
1-Nitro-3-(phenylethynyl)benzene (**5c**)	1.97	C1, π (*m*NO_2Ph)	50.51 %	0.007
		C2, π (Ph)	49.49 %	0.034
	1.87	C1, π (*m*NO_2Ph)	50.95 %	
		C2, π (Ph)	49.04 %	
1,2-Bis(4-nitrophenyl)ethyne (**5f**)	1.97	C1, π (*p*NO_2Ph)	50.00 %	0.031
		C2, π (*p*NO_2Ph)	50.00 %	0.033
	1.85	C1, π (*p*NO_2Ph)	50.00 %	
		C2, π (*p*NO_2Ph)	50.00 %	
1-Methoxy-4-((4-nitrophenyl)ethynyl)benzene (**5e**)	1.97	C1, π ($PhNO_2$)	50.04 %	−0.011
		C2, π (PhOMe)	49.96 %	0.056
	1.85	C1, π ($PhNO_2$)	51.93 %	
		C2, π (PhOMe)	48.08 %	
4-(Phenylethynyl)pyridine (**7a**)	1.97	C1, π (4-Py)	50.01 %	−0.016
		C2, π (Ph)	49.98 %	0.055
	1.86	C1, π (4-Py)	51.05 %	
		C2, π (Ph)	48.94 %	
2-(Phenylethynyl)pyridine (**7b**)	1.96	C1, π (2-Py)	49.87 %	0.008
		C2, π (Ph)	50.13 %	0.013
	1.86	C1, π (2-Py)	50.81 %	
		C2, π (Ph)	49.18 %	
2-(Phenylethynyl)anthracene-9,10-dione (**1b**)	1.97	C1, π (Anth)	50.17 %	0.001
		C2, π (Ph)	49.83 %	0.031
	1.85	C1, π (Anth)	51.07 %	
		C2, π (Ph)	48.94 %	

[A]Functional groups in parentheses indicate which carbon of the alkyne is being referred to, C1 or C2.
[B]c_A^2 = polarization coefficient squared.



Scheme 11. Use of cross-coupling and fragmentation strategies for the introduction of methyl and imidazoline groups to aromatics. EAG = electron accepting group.

*1,4-Dimethyl-2-nitro-5-(phenylethynyl)benzene (**5b**)*

Yield 80 %, mp 86–88°C (hexane). δ_H ($CDCl_3$, 400 MHz) 2.54 (s, 3H, *m*-Me), 2.57 (s, 3H, *o*-Me), 7.39 (m, 3H, Ph), 7.45 (s, 1H, *m*-H_{Ar}), 7.55 (m, 2H, Ph), 7.89 (s, 1H, *o*-H_{Ar}). δ_C ($CDCl_3$, 100 MHz) 20.22, 20.31 (2Me), 86.72, 97.39 (C≡C), 122.63, 125.65, 128.67, 129.21, 131.14, 131.86, 135.87, 139.14 (C_{Ar}), 147.94 (C–NO_2). ν_{max} (KBr)/cm^{-1} 1340, 1517 (NO_2), 2208 (C≡C). Found: C 76.60, H 5.23, N 5.41. $C_{16}H_{13}NO_2$ requires C 76.48, H 5.21, N 5.57 %.

*1-Nitro-3-(phenylethynyl)benzene (**5c**)*

Yield 70 %, mp 67–69°C (lit. 68–70°C[22]).

*1-Methoxy-4-nitro-2-(phenylethynyl)benzene (**5d**)*

Yield 75 %; the product was obtained as a yellow oil.[23] δ_H ($CDCl_3$) 3.89 (s, 3H), 6.94 (d, *J* 9.2, 1H), 7.30–7.32 (m, 3H), 7.53–7.55 (m, 2H), 8.20 (dd, *J* 9.2, 2.8, 1H), 8.40 (d, *J* 2.4, 1H). ν_{max} (KBr)/cm^{-1} 2225 (C≡C).

*1-Methoxy-4-((4-nitrophenyl)ethynyl)benzene (**5e**)*

Yield 83 %, mp 121–123°C (lit. 122–124°C[24]).

*1,2-Bis(4-nitrophenyl)ethyne (**5f**)*

Yield 67 % mp 219–220°C (lit. 221–221.5°C[24]).

*1-Methoxy-4-(phenylethynyl)benzene (**5g**)*

Yield 52 %, mp 61–62°C (lit. 63–64°C[24]).

*4-(Phenylethynyl)pyridine (**7a**)*

Yield 68 %, mp 90–92°C (lit. 92–93°C[25]).

*2-(Phenylethynyl)pyridine (**7b**)*

Yield 78 %, mp 31°C (lit. 32°C[26]).

Table 2. Reaction yields and product melting points

Starting alkyne	Duration of reaction [h]	Products	Yield [%]	Melting point [°C]
1a	3	**2a**	69	172–173 (lit. 173[27])
		3a	68	93–95 (lit. 92–94[28])
		4	12	204–205 (lit. 207–208[29])
1b	5	**2b**	94	175–177 (lit. 176–176.5[30])
		3a	93	92–94 (lit. 92–94[28])
5a	3	**6a**	68	53–54 (lit. 51–55[31])
		3a	61	93–95 (lit. 92–94[28])
5b	6	**6b**	87	64–66 (lit. 70–70.5[32])
		3a	81	94–95 (lit. 92–94[28])
5c	40	**5c**	80	66–68 (lit. 68–70[22])
5d	4	**8**	74	120–122
5e	8	**6a**	62	52–54 (lit. 51–55[31])
		3b	66	136–138 (lit. 138–139[33])
5f	1	**6a**	51	51–52 (lit. 51–55[31])
		3c	55	241–243 (lit. 242–243[33])
5g	50	**5g**	85	60–62 (lit. 63–64[23])
7a	40	**9**	27 (GC-MS)	Not isolated
		3a	70	91–93 (lit. 92–94[28])
7b	40	**10**	48 (GC-MS)	Not isolated
		11	42 (GC-MS)	Not isolated

Reaction of Alkynes with Ethylenediamine – General Procedure

A mixture of alkyne **1a–b, 5a–g, 7a–b** (1.6 mmol) and ethylenediamine (5 ml, 75.0 mmol) in pyridine was refluxed for 1–50 h. Solvent was removed under reduced pressure and the crude reaction mixture was purified by column chromatography (toluene/ethyl acetate) to give pure products (Table 2).

In the case of 2-(phenylethynyl)pyridine (**7b**), the reaction mixture was treated with an ethanolic solution of 2,4-dinitrophenylhydrazine to afford (*Z*)-2-(2-(2-(2,4-dinitrophenyl) hydrazono)-2-phenylethyl)pyridine; yield 35 %, mp 196–198°C (lit. 192–194°C[34]).

Supplementary Material

NMR data and conditions for the reactions of **5d** and **7a** with ethylenediamine and the optimized energies and geometries of starting materials are available on the Journal's website.

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