ChemComm

COMMUNICATION

COYAL SOCIETY OF CHEMISTRY

View Article Online

Cite this: DOI: 10.1039/c3cc47707j

Received 9th October 2013, Accepted 13th January 2014

DOI: 10.1039/c3cc47707j

www.rsc.org/chemcomm

Convenient one-step construction of yne-functionalized aryl halides through domino cyclization from tetraynes[†]

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An efficient method for the construction of fused yne-substituted aryl halides by reaction of unactivated linear tetraynes with allyl halides *via* domino C–C coupling and formation of C–X bonds in the presence of $Pd(OAc)_2/PPh_3$ was developed.

Aryl halides have attracted considerable attention in organic synthesis and their chemistry is being actively explored in synthetic transformations.¹ Fused aryl halides represent an interesting structural motif frequently found in various bioactive molecules and functional materials.² Although numerous fused heterocycles containing halogens have been characterized and used in various applications, few reports on fused vne-functionalized aryl halides are available.³ This may be partly due to the fact that these compounds cannot be prepared efficiently using current methods, the formation of carbon-halogen bonds in complex molecules is still a significant challenge.4 Hoye reported a variety of hexadehydro-Diels-Alder (HDDA) cascade reactions to construct complex benzenoids through aryne intermediates.⁵ Lee and co-workers developed catalytic alkane C-H insertion, forming carbon-carbon bonds, to convert tetrayne into yne-functionalized tricyclic compounds.⁶ Ishihara developed a method for the halocyclization of homo-(polyprenyl)arenes using nucleophilic promoters.⁷ Hayashi reported on the ruthenium-catalyzed transformation of aryl and alkenyl triflates to halides.⁸ As we know, fused arylhalides can be used as substrates in the Heck reaction to design building blocks for pharmaceutically and biologically active substances.9,10 Both aromatics and acetylenes have been successfully used in extended π systems for organic electronic materials. The fluorene and phenanthrene frameworks are synthesized through exclusive

5-*exo*- and 6-*endo*-dig hydroarylation from *o*-alkynyl biaryls as starting materials.¹¹ In our current work, we developed the first simple synthesis of aryl halides through tetrayne systems *via* domino cyclization.¹² This process exhibits excellent regioselectivity to produce highly substituted fused bicyclic 2,3-dihydro-1*H*-indene under mild reaction conditions with good to excellent yields. We have studied the palladium-catalyzed reactions of dimethyl 2,2-bis(5-phenylpenta-2,4-diyn-1-yl)malonate (**a**–**l**) with different allyl halides, which provide a direct, efficient, and economical methodology for the construction of fused yne-functionalized aryl halides through successive C–C coupling patterns of the products with unexpected C–X coupling reactions.

A survey of the reaction conditions using **b** and allyl bromide as a test experiment was performed (Table 1). The efficiency of the domino reaction can be enhanced by increasing the reaction temperature to 100 °C. The bases play an important role in the overall efficiency of this domino reaction, by simply varying the bases from potassium carbonate to tributylamine under otherwise identical conditions as well as furnishing the excited diethyl 7-bromo-5-phenyl-4-(phenylethynyl)-1H-indene-2,2(3H)-dicarboxylate (ba) with 90% yield. Among the catalysts investigated, the palladium(II) acetate/PPh3 catalytic system was found to be the most effective in the cross-coupling reactions screened, DMF proved to be a better solvent than toluene. If NaI or NaBr or Bu₄NBr were used as the halide source instead of allyl bromide, the reaction could not be performed. If allyl chloride was used in combination with Bu₄NBr (or allyl bromide with Bu₄NCl) to provide the halogen species, the reactions provided the normal yne-functionalized aryl halides in which the halides came from allyl halides without any scrambling of the halides in the products. Thus, the following standard reaction conditions were used to carry out the following studies: 1 equiv. of b was reacted with 1.2 equiv. of allyl bromide and water in the presence of 2 mol% of palladium(II) catalyst, and 4 mol% PPh₃ with nBu_3N (2 equiv.) as an additive in DMF at 100 °C.

Illustrative examples of the scope of this study are shown in Table 1. Interestingly, various substituted tetraynes were compatible with this palladium-catalyzed domino reaction. A range of 7-halide-5-phenyl-4-(phenylethynyl)-1*H*-indene-2,2(3*H*)-dicarboxylate compounds

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[†] Electronic supplementary information (ESI) available: Experimental procedures and characterization of all new compounds. CCDC 901558–901560. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/ c3cc47707j

yne-functionalized aryl halides from tetraynes ^a							
	R 	R 	AllyIX, Pd(nBu₃N (OAc)₂	Y	×	
			DMF/H ₂ 12	O, 100 ^o C 2h			R
a - I						R aa - Ib	
Entry	S	Y/R			Х	Product	Yield ^b (%)
1	a	Y = C(CC)	$OOMe)_2; R =$	= Ph	Br	aa	84
2	b	Y = C(CC)	$OOEt)_2; R =$	Ph	Br	ba	90
3	b	Y = C(CC)	$OOEt)_2; R =$	Ph	Cl	bb	89
4	b	Y = C(CC)	$OOEt)_2; R =$	Ph	Ι	bc	77
5	с	Y = (MeC)	DC)C(COOE	Et); R = Ph	Br	ca	76
6	с	Y = (MeC)	DC)C(COOE	Et; $R = Ph$	Cl	cb	85
7	с	Y = (MeC)	COOE	Et); R = Ph	Ι	сс	80
8	d	Y = C(CC)	$O^{i}Pr)_{2}; R =$	Ph	Br	da	88
9	d	Y = C(CC)	$OO^{i}Pr)_{2}; R =$	= Ph	Cl	db	84
10	e	Y = C(CC)	$OOEt)_2; R =$	<i>p</i> -MeOC ₆ H ₄	Br	ea	83
11	e	Y = C(CC)	$OOEt)_2; R =$	<i>p</i> -MeOC ₆ H ₄	Cl	eb	86
12	f	Y = C(CC)	$OO^{1}Pr)_{2}; R =$	$= p-MeOC_6H_4$	Br	fa	80
13	g	Y = C(CC)	$OOEt)_2; R =$	p-MeC ₆ H ₄	Br	ga	85
14	h	Y = C(CC)	$OOEt)_2; R =$	p-EtOC ₆ H ₄	Br	ha	85
15	h	Y = C(CC)	$OOEt)_2; R =$	p-EtOC ₆ H ₄	Cl	hb	73
16	i	Y = C(CC)	$OOEt)_2; R =$	p-FC ₆ H ₄	Br	ia	77
17	j	Y = C(CC)	$OO^{i}Pr)_{2}; R =$	$= p - ClC_6H_4$	Cl	ja	75
18	k	Y = NTs;	R = Ph		Br	ka	87
19	1	Y = NTs;	$\mathbf{R} = n\mathbf{B}\mathbf{u}$		Br	la	84
20	1	Y = NTs;	R = nBu		Cl	lb	82

 Table 1
 Palladium-catalyzed domino reaction for the formation of fused vne-functionalized aryl halides from tetraynes^a

^{*a*} General conditions: **a**-**l** (1.0 equiv.), AllylX (X = Cl; Br; I) (1.2 equiv.), H_2O (1.2 equiv.), Pd(OAc)₂ (2 mol%), PPh₃ (4 mol%), *n*Bu₃N (2 equiv.), DMF 10 mL, 100 °C. ^{*b*} Isolated yield after flash column chromatography.

were readily isolated with good to excellent yields when tetraynes with a variety of substituted groups were employed. The substituted groups could be methoxy, methyl, ethyl, bromo, or chloro groups. Using substituted tetraynes (**c**, **d**, **e**, **g**) as substrates with allyl chloride or allyl bromide or allyl iodide, the reactions afforded 7-halo-5-phenyl-4-(phenylethynyl)-1*H*-indene-2,2(3*H*)-dicarboxylate in good yields (Table 1, for example, **cb**, **da**, **eb** and **ga**). The compounds **ba** and **bb** had the highest isolated yields, 90% and 89%, respectively. Moreover, the cyclic compound **ka** from reaction of 4-methyl-*N*,*N*-bis(5-phenylpenta-2,4-diyn-1-yl)benzenesulfonamide (**k**) and allyl bromide also has a high yield (Table 1, entry 18) of 87%. Substrates containing alkyl groups (Table 1, entries 19, 20) instead of phenyl or substituted phenyl groups also produced good yields.

All new products were fully characterized by various spectroscopic techniques and high-resolution mass spectrometry, and the molecular structures of **ba**, **bb** and **hb** (Fig. 1), were confirmed using single-crystal X-ray analyses (see the ESI[†] for details).¹³

A plausible mechanism for the formation of fused ynefunctionalized aromatic halides is depicted in Scheme 1. Oxidative coupling of Pd(0) in the tetrayne moiety (1) produces the Pd(II) intermediate **A**, **A** generates a seven-member ring, **B**. **B** undergoes reductive elimination coupling to afford Pd(0) (C),¹⁴ C then reacts with allylic bromide and H_2O^{15} to produce **D**, which undergoes reductive elimination to produce the final products and Pd(0).



Fig. 1 Molecular structure of **hb** with ellipsoids drawn at 50% probability. Hydrogen atoms are omitted for clarity.



In summary, we have developed an easy method to construct fused yne-functionalized aryl halides through tetrayne systems via domino cyclization. This reaction exhibited an excellent regioselectivity, producing highly substituted fused yne-functionalized bicyclic compounds under mild reaction conditions with good to excellent yields in the presence of the amine and palladium(π) acetate/PPh3 catalytic system. To the best of our knowledge, no study on such fused benzene halide cores has been reported with this methodology, a topic which could be of interest among researchers in the field. The generality of this process also makes the reaction highly valuable due to the synthetic and medicinal importance of these unsaturated polycyclic compounds. This preliminary work has broad implications and may serve as a seminal study toward the catalytic synthesis of aromatic halides with unactivated olefins. In addition, the construction of the C-X bond followed by successive C-C coupling may have potential application for direct halogenation of unsaturated hydrocarbons. Further mechanistic studies and

development of the related domino inter-intramolecular reactions are currently ongoing.

The authors thank the National Natural Science Foundation of China (21272005, 21072003, 21372010), National Basic Research Program of China (No. 2012CB821600), and Department of Human Resources of Anhui Province for financial support.

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- 15 When deuterated DMF was used as a solvent for the reaction, no deuterated product was observed, indicating that DMF did not take part in the reaction. A deuterated product was isolated when the reaction was performed with a mixed solvent of DMF and a small amount of deuterated water (D_2O) (comparison of ¹H NMR of **la** with **lc**, see ESI[†]).