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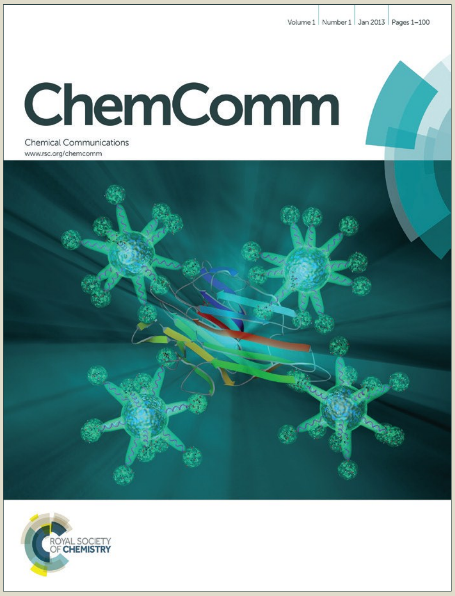

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ARTICLE

Metal-Free Arylation of Pyrimidines Through Photochemical Process

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Pyrimidinyl and pyrazinyl radicals were generated under moderate energetic irradiation conditions (UVA), and proved to be prompt to undergo C-C bond formation processes. Hetero-biaryl derivatives were obtained in good to high yields with highly interesting functional group selectivities. Bis hetero-biaryls were also easily accessible leading to original compounds, ready for further transformations. Experiments supporting radical processes have been reported.

Introduction

Diazines are ubiquitous scaffolds found in life and material science and also extensively represented among natural products and pharmaceuticals. [1,2,3] Based on their large field of application, the development of new processes that allow versatile chemical alteration of diazines under mild conditions is of primary importance. Moreover, economical and environmental issues have to be considered. The construction of diazine skeletals are generally dedicated to early steps synthesis of complex molecules.[4] To improve the flexibility of synthetic pathways, late derivatization of such scaffolds might be more suitable.

Diazines are electron-deficient heteroarene having a low energy LUMO. For this reason, nucleophilic aromatic substitution (SNAr) has been intensively used as a functionalization pathway. However, a stoichiometric amount of strong base and the need of directing and protective groups are important limitations.[5,6] C-C Bond formation involving C-X partners using a catalytic organometallic process is a valuable alternative but the C-H activation of electron-deficient (hetero)arenes still requires improvements.[7,8] Radical functionalizations of diazines, and particularly pyrimidines, have been reported with heteroarenes serving as acceptors for carbon-centered radicals according to Minisci or Gomberg–Bachmann type reactions, known to proceed with low regioselectivities.[9,10] Then, the selectivity can be enhanced by generating a radical center at the suitable position of the diazine moiety. While pyridyl radicals have been studied widely,[11] only a few publications deal with pyrimidinyl and pyrazinyl radicals, and most of them involve the use of tin or silanes derivatives as the radical chain mediator.[12,13] To develop mild and sustainable C-C bond formation on pyrimidines and pyrazines, photochemistry is certainly a valuable alternative to the overstoichiometric use of radical chain mediators or toxic tin derivatives. UV irradiation has been used for the formation of aryl radicals.[14,15] Surprisingly, only one publication reports the photolysis of 5-iodopyrimidine with a low-pressure mercury arc at 254 nm and the trapping of the resulting radical with heteroaromatic compounds.[16] This transformation is limited to the photolysis of C-I bond under high energy irradiation. Such process would have strong synthetic impact if it could proceed with lower energy light and a broader scope of substrates.

Results and Discussion

We decided to investigate versatile and mild photochemical transformations of pyrimidines dedicated to C-C bond formation and focused on heterobiaryl scaffolds. In a first task, 5-bromopyrimidine **1** was used for optimization of the photochemical arylation. Irradiation was conducted in a Rayonet photoreactor at 254, 300 and 350 nm or with a medium-pressure mercury-vapors lamp (100 W) equipped with an anticaloric filter (338-500 nm, UV-A/visible, see SI) (Table 1). The latter proved to be the most efficient and versatile irradiation system. By using acetonitrile as solvent in the presence of 20 equivalents of benzene, 5-phenylpyrimidine **2a** was obtained in 27% yield (Table 1, entry 1). Use of THF, DMF, DMSO, MeOH, AcOEt and *t*BuOH did not improve the arylation outcome. Slight improvements were observed in DCM/ACN mixture (95/5 v/v) furnishing **2a** and **2b** in 41 and 31% yield (Table 1, entries 2-3).

We checked the influence of basic additives to trap the released HBr and facilitate the aromatization step (Table 1, entries 4-5 and SI). With K_2CO_3 (3 equiv.), **2b** was obtained in 47% yield. Comparable results were observed in acetonitrile (Table 1, entry 6) and with only 1.1 equivalent of K_2CO_3 (Table 1, entry 7). Moreover, we were able to decrease the amount of the acceptor from 20 to 10 equivalents with even better yields of **2b** (54%) and **2a** (67%) (Table 1, entries 8-9). Light is crucial while no reaction was observed in the dark (Table 1, entry 10). At this point, a direct nucleophilic substitution of 5-bromopyrimidine can be excluded.

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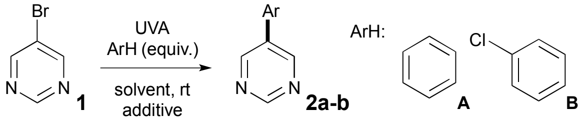
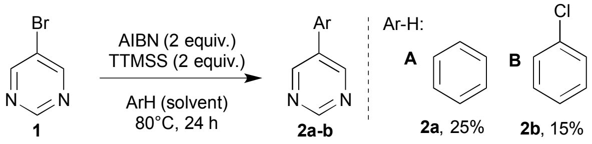
Table 1. Optimization of the photoarylation method.



Entry	ArH (equiv.)	solvent	Additive	Yield (%)[c-d]
1	A (20)	ACN	-	27
2	A (20)	CH_2Cl_2/ACN[a]	-	41
3	B (20)	CH_2Cl_2/ACN [a]	-	31
4	B (20)	CH_2Cl_2/ACN [a]	K_2CO_3 (3)	47
5	B (20)	CH_2Cl_2/ACN [a]	Cs_2CO_3 (3)	42
6	B (20)	ACN	K_2CO_3 (3)	50
7	B (20)	ACN	K_2CO_3 (1.1)	51
8	***B (10)***	***ACN***	***K_2CO_3 (1.1)***	***54***
9	***A (10)***	***ACN***	***K_2CO_3 (1.1)***	***67***
10	A (10)	ACN	K_2CO_3 (1.1)	0[b]

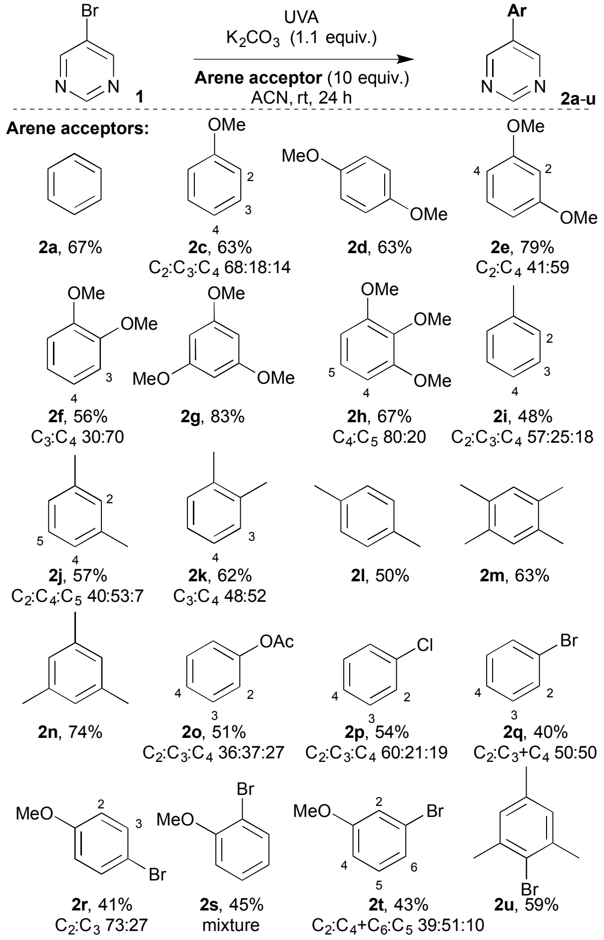
[a] CH_2Cl_2/MeCN 95/5 (v/v). [b] Reaction was conducted in the dark. [c] Irradiation was done with a medium-pressure mercury lamp (100 W) with an anticaloric filter (338-500 nm). [d] See Scheme 2 for regioselectivity with B.

In our hands, this photoarylation process proved to be superior to classical radical chain reaction using TTMSS/AIBN system (Scheme 1). **2a** and **2b** were formed in low yields and isolated from complex mixtures.



Scheme 1. TTMSS/AIBN conditions for arylation of **1**.

The optimized conditions were applied to the photoarylation of pyrimidine with various aromatic acceptors (Scheme 2). Methoxy-substituted arenes were engaged in this process to afford the corresponding 5-aryl-pyrimidines in good to high yields. With anisole, **2c** was obtained in 63% yield as a mixture of regioisomers (C_2:C_3:C_4 68:18:14). This regioselectivity is consistent with the addition of the 5-pyrimidinyl electrophilic radical onto an electron-rich arene. 1,2- and 1,4-Dimethoxybenzene reacted in a similar manner to afford **2f** and **2d** in good yields. When electron-rich trimethoxybenzene acceptors were used, the arylation process proved to be very efficient since **2g** was obtained in 83% yield. Similar behaviour was observed within the series of methyl-substituted arenes. Regioisomeric mixtures were isolated with toluene, *ortho*- and *meta*-xylene but still in good yields. 5-Pyrimidinyl radical reacted more efficiently with nucleophilic durene and mesitylene to afford **2m** and **2n** in 63% and 74% yields respectively. Under our conditions, polymethyl-substituted arenes, which are good hydrogen atom donors, were valuable radical acceptors. Ester group (**2o**) and chloride (**2p**) were also tolerated as substituent of the acceptor. Interestingly, aryl bromides were advantageously engaged in the photochemical arylation reaction. The selective cleavage of the 5-bromopyrimidine C-Br bond has been done in the presence of other aryl C-Br bond to form exclusively the 5-pyrimidinyl radical which added onto the aryl bromide acceptor (**2q-u**). This selectivity allowed a one-step synthesis of biaryl pyrimidine derivative having an aryl bromide function readily available for further transformations like cross coupling reaction. The yields were moderate to good as 59% of **2u** was isolated.



Scheme 2. Photoarylation of 5-bromopyrimidine.

This synthetically usefulness of our method was illustrated by the selective functionalization of **3** possessing two reactive C_{sp2}-Br bonds (Scheme 3). Under the standard conditions, **3** was irradiated in the presence of 1,3,5-trimethoxybenzene. After 24 h, a conversion of 60% was observed and **4** was isolated in 44% yield without any traces of arylation product at the phenyl ring.

Then, we extended the scope of the photoarylation to substituted diazines (Scheme 4). 2-Fluoro-5-bromopyrimidine **1b** was engaged under standard conditions in the presence of arene acceptors. High yields of 2-fluoro-5-aryl-pyrimidine

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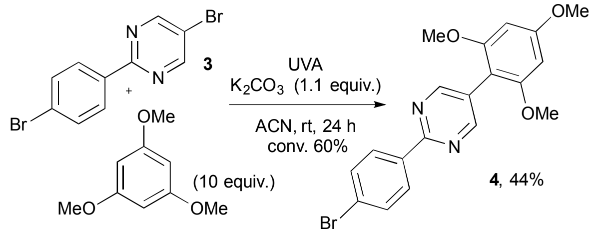
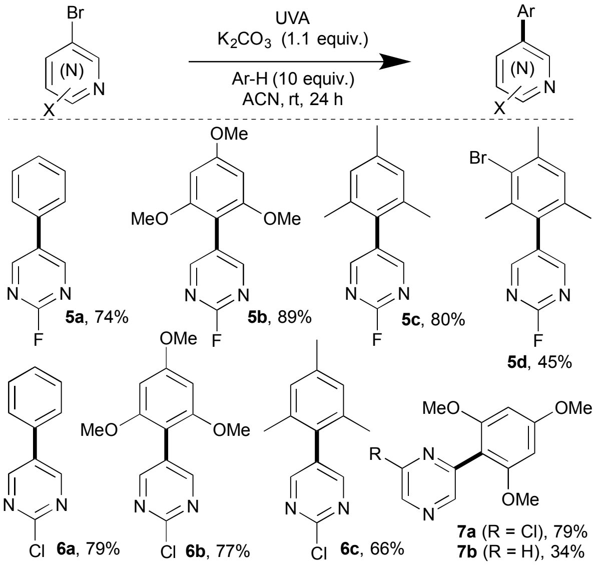
derivatives were obtained with benzene (**5a**, 74%), 1,3,5-trimethoxybenzene (**5b**, 89%) and mesitylene (**5c**, 80%). With 2,4,6-trimethybromobenzene, **5d** was isolated in 45% yield through a selective photochemical activation of the C-Br bond from pyrimidine **1b**. 2-Chloro-5-bromopyrimidine **1c** was also an interesting partner since the corresponding phenyl (**6a,** 79%), 2,4,6-trimethoxyphenyl (**6b,** 77%) and 2,4,6-trimethylphenyl (**6b,** 66%) derivatives were isolated in good to high yields.



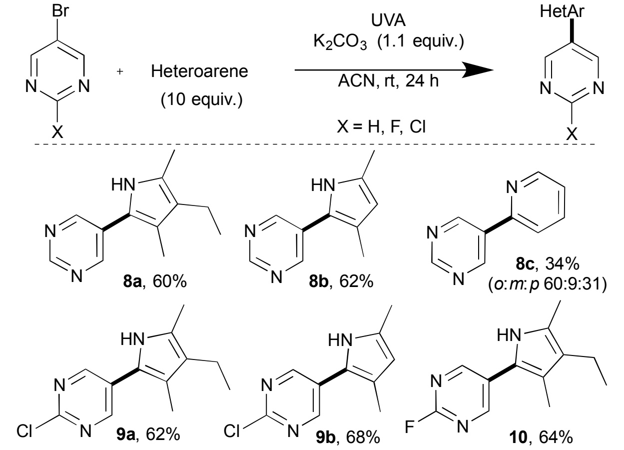
Scheme 3. Selective C-Br bond cleavage in photoarylation conditions.



Scheme 4. Photoarylation of substituted diazines.

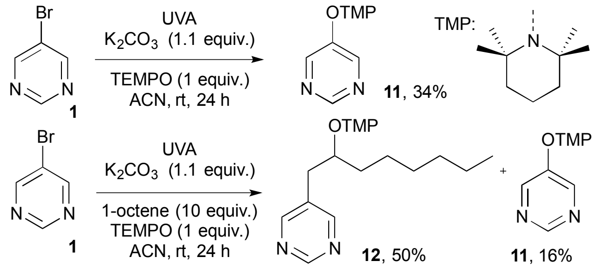
To our delight, the photoarylation method succeeded also with pyrazine scaffold since 2-bromo-6-chloropyrazine was smoothly arylated to afford **7a** in 79% yield. Unfortunately, 2-bromopyrazine gave the corresponding biaryl compounds in lower yield. From a synthetic point of view, this selective arylation process opens interesting opportunities for the construction of valuable heterobiaryl scaffolds through ionic or organometallic coupling reactions of the resting C-F, C-Cl or C-Br bond.

One step further was to delineate the scope of arylation with heteroaromatic acceptors (Scheme 5). We focused on nitrogen-containing heteroarenes because they are key building blocks for pharmaceutical, agrochemical and materials chemistry.



Scheme 5. Photoarylation with heteroaromatic partners.

2,4-Dimethyl-3-ethylpyrrole (kryptopyrrole) and 2,4-dimethylpyrrole were engaged in the photoarylation process with 5-bromopyrimidine **1**. Indole and Benzofuran have aslo been investigated as radical acceptors but afforded mixture of arylation products. Compounds **8a** and **8b** were isolated in 60% and 62% yield respectively. The selective formation of **8b** is in agreement with the generally observed radical addition at the 2-position of pyrrole derivatives.[17] The radical addition of the 5-pyrimidinyl radical onto pyridine gave **8c** in a low yield (34%). This can be explained by the electro-deficient character of the pyridine which does not fit in term of polar effect with the electrophilic pyrimidinyl radical. In contrary, good yields were obtained with 2-chloro- and 2-fluoro-5-bromopyrimidine with similar selectivity. It is noteworthy that free pyrrole derivatives were smoothly substituted under the conditions while ionic or organometallic transformations generally require a nitrogen protective group.



Scheme 6. Direct radical trapping experiment and tandem radical addition/trapping.

To gain insight into the mechanism, we carried out radical trapping experiments (Scheme 6). 5-Bromopyrimidine **1** was irradiated under typical conditions in the presence of TEMPO (1 equiv.). Adduct **11** was isolated in 34% yield, what strongly supports the formation of free 5-pyrimidinyl radical, subsequently trapped by TEMPO. The lower efficiency of this reaction could be explained by a low reaction rate of coupling two electrophilic radicals. When 1-octene was added to the reaction mixture, the 5-pyrimidinyl radical added first onto the olefin and the resulting secondary alkyl radical was trapped by

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TEMPO to afford **12** in 50% yield. Side product **11**, resulting from the direct radical trapping was isolated in 16% yield. This important reaction supports again a radical process and opens new perspectives for the formation of Csp2-Csp3 bond under these photochemical conditions.

Conclusions

We developed an efficient process for the photoarylation of pyrimidine derivatives under mild UVA irradiation with K_2CO_3 as the sole additive. We demonstrated that valuable heteroaryls and bisheteroaryls can be obtained in good to high yields under these conditions from commercially available substrates without the need of modification. The high selectivity of the reaction toward halogen-substituted substrates or acceptors makes this transformation valuable for further and/or late functionalization and suitable as key step in total synthesis. The photoarylation mechanism is under investigation according to recent investigation in the field and will be reported in a due course.[18]

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