Tetrahedron Letters 56 (2015) 2827–2831

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Facile Pd-catalyzed amination of imidazolin-1-yl chloroazines under microwave irradiation: toward a new kinase-inhibitory chemotype

Prashant Mujumdar [a], Pakornwit Sarnpitak [a], Anton Shetnev [b], Mikhail Dorogov [b], Mikhail Krasavin [c,*]

[a] Eskitis Institute for Drug Discovery, Griffith University, Nathan, Queensland 4111, Australia
[b] The Ushinsky Yaroslavl State Pedagogical University, 108 Respublikanskaya St., Yaroslavl 150000, Russian Federation
[c] Institute of Chemistry, St. Petersburg State University, 26 Universitetskyi Prospekt, Peterhof, 198504, Russian Federation

ARTICLE INFO

Article history:
Received 10 February 2015
Revised 13 April 2015
Accepted 16 April 2015
Available online 20 April 2015

Keywords:
2-Imidazoline
Chemical instability
Microwave irradiation
Buchwald–Hartwig amination
Kinase inhibitors
Hinge region binders

ABSTRACT

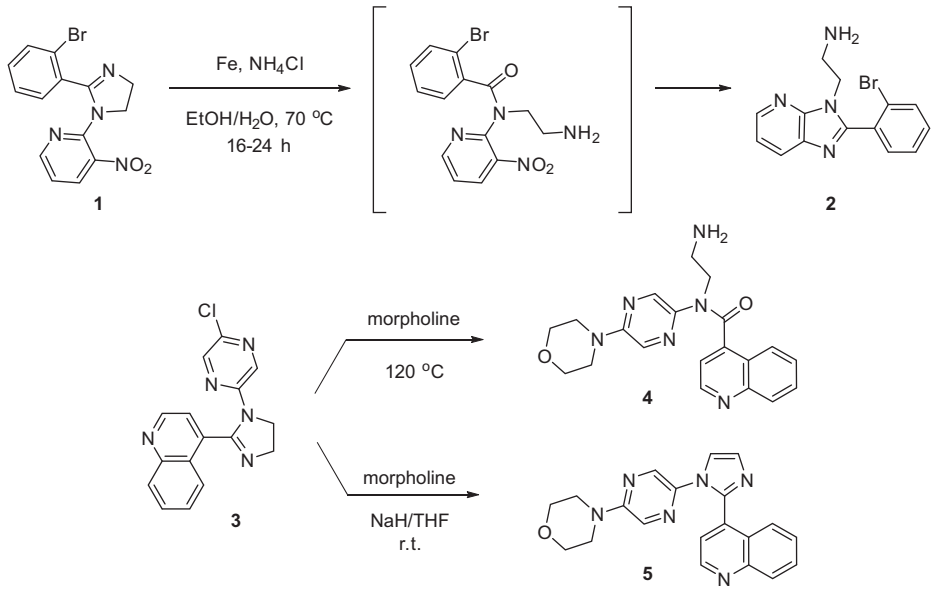
The imidazolin-1-yl azine moiety, constructed using a recently developed Buchwald–Hartwig-type arylation methodology, displays excellent chemical stability under subsequent microwave-assisted Pd-catalyzed amination with a range of *N*-nucleophiles. This finding extends the usage of imidazolin-1-yl azines for bioactive compound library design. The latter is exemplified herein by the discovery of micromolar kinase inhibitors.

Recently, we developed a Pd-catalyzed protocol to efficiently arylate 2-imidazolines with various haloazines and electron-deficient haloaromatics.[1] Since then, we have developed a new series of orally available, efficacious anti-inflammatory inhibitors of cyclooxygenase-2 utilizing said protocol.[2] At the same time, several examples of the chemical instability of the poorly studied imidazolin-1-yl azine moiety have surfaced. Under Bechamp reduction conditions (Fe, NH_4Cl, EtOH/H_2O, 70 °C, 16 h), *N*-(pyrid-2-yl)imidazolines **1** underwent an unexpected hydrolytic ring-opening, which found utility as an unusual entry into imidazo[4,5-*b*]pyridines **2**.[3] Furthermore, attempts to perform direct nucleophilic aromatic substitution of *N*-(haloazine)imidazolines like **3** with morpholine either led, under thermal conditions, to the formation of the ring-opened product **4** or triggered, in the presence of NaH, aromatization to give imidazole **5** (Scheme 1).[4] In our initial report on imidazoline N-arylation,[1] we provided three pilot examples indicating that compounds such as **3** could be substrates for further Pd-catalyzed coupling reactions with either another 2-imidazoline or a secondary amine. No damage to the imidazoline core was observed which was significant, in light of the known tendency of 2-imidazolines[5] as well amidines in general[6,7] to undergo transamination with various amines. Considering the importance of such a modification for the generation of a library based on the imidazolin-1-yl azine core, we sought to ascertain a broader scope for the Pd-catalyzed amination of imidazolin-1-yl azines, employing various azine linkers and a range of *N*-nucleophiles. Unfortunately, the prolonged time required for these reactions to go to completion under conventional heating,[1] hinders performing them in an array format. Therefore, we also aimed to evaluate the amination of 2-imidazoline-containing chloroazines under microwave irradiation[8] to achieve shorter reaction times. This strategy was expected to have some risk, considering reports that microwave irradiation can significantly facilitate the transamination of amidines.[9] Herein, we report the results of these studies and solid evidence of the scaffolds being chemically compatible with microwave-assisted Buchwald–Hartwig-type amination. In addition, we have investigated this chemotype in the context of designing novel, therapeutically relevant kinase inhibitors.

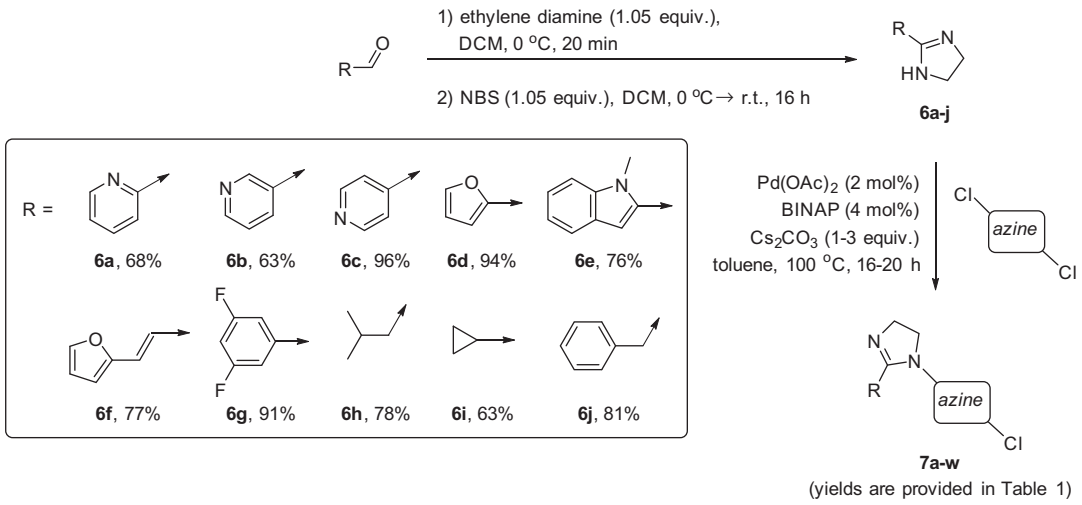
Using the robust protocol of Fujioka et al.,[10] we prepared ten 2-imidazolines **6a–j** and *N*-arylated them, on 300–500 mg scale, with various dichloroazines, using the earlier published protocol employing conventional heating.[1] While the yields of 2-imidazolines from their respective aldehydes have already been noted as being good to excellent,[1,3] we were also pleased to find the yields of the arylation step to be quite satisfying and chromatographic purification of the respective imidazolin-1-yl azine products **7a–w** to be rather straightforward (Scheme 2, Table 1). With the twenty-three substrates **7a–w** at hand, we proceeded to undertake

* Corresponding author. Tel.: +7 931 3617872; fax: +7 812 428 6939.
E-mail address: m.krasavin@spbu.ru (M. Krasavin).

http://dx.doi.org/10.1016/j.tetlet.2015.04.059
0040-4039/



Scheme 1. Illustrative cases of the chemical instability of imidazolin-1-yl azines.



Scheme 2. Preparation of the starting materials **7a**–**w** for the subsequent Buchwald–Hartwig coupling study.

a broader survey of Buchwald–Hartwig-type couplings with various *N*-nucleophiles, in order to establish the chemical compatibility of the imidazolin-1-yl azine cores with this reaction (Scheme 3). Gratifyingly, the reactions proceeded to completion on 3–5 mmol scale in much shorter times (40–60 min) compared to conventional heating, with no appreciable degradation of the 2-imidazoline core. This allowed us to obtain novel, diversely substituted compounds **8a**–**w** in good yields after simple chromatographic purification (Table 1).[11] From their spectroscopic data, it was evident the imidazolin-1-yl azine core remained intact in all products **8a**–**w**. Interestingly, attempted preparation of the symmetrically substituted bis-imidazolinyl azines (**8d**, **8f**, **8k**) in one step, via the use of 2 equiv of the respective 2-imidazolines (**6c**, **6d**, **6h**) resulted in complex product mixtures, under conventional heating or microwave irradiation alike. Therefore, stepwise introduction of imidazoline moieties into the dihaloazine core appears to be essential.

Mostly associated with the modulation of adrenergic and imidazoline receptors,[12,13] 2-imidazoline-containing compounds cover a large biological space and are a privileged[14,15] class of compounds.[16] However, kinase inhibition has not been documented for compounds based on the 2-imidazoline scaffold. We were puzzled by the lack of such reports in the literature, attributing this to the novelty of the imidazolin-1-yl azine chemotype. Indeed, with the highly polar, nitrogen-rich molecular framework, compounds **8a**–**w** were likely to be good candidates for forming hydrogen-bonding interactions with the hinge region of protein kinases.[17] In order to verify this hypothesis without undertaking a massive library synthesis and a laborious screening exercise, we diluted our pilot library **8a**–**w** into a larger virtual library of 1235 diverse compounds of the same general structure and undertook an in silico docking prioritization of these compounds against a panel of human kinases, followed by Tanimoto similarity clustering of the virtual hits (this work will be subject to a separate disclosure).[18] As the result of this effort, compounds **8i**, **8j**, **8m**, **8q**, and **8r** emerged as representatives of the highest-scoring clusters.[19] These compounds were screened against a panel of 48 human kinases provided by Cerep (France).[20] The 240 data points collected for the five compounds revealed that three of the five compounds tested exhibited >30% inhibition of only a few