Tetrahedron Letters xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Benzo[4,5]imidazo[2,1-*b*]quinazolin-12-ones and benzo[4,5]imidazo-[1,2-*a*]pyrido[2,3-*d*]pyrimidin-5-ones by a sequential N-acylation–S_NAr reaction

Krishna Kumar Gnanasekaran, Nagendra Prasad Muddala, Richard A. Bunce *

Department of Chemistry, Oklahoma State University, Stillwater, OK 74078-3071, USA

ARTICLE INFO

Article history:
Received 6 October 2015
Revised 10 November 2015
Accepted 12 November 2015
Available online xxxx

Keywords:
Benzimidazoquinazolinones
Acylation–S_NAr reaction
Sequential reactions
Tautomerism
Heterocycles

ABSTRACT

An efficient synthesis of benzo[4.5]imidazo[2,1-*b*]quinazolin-12-ones and benzo[4,5]imidazo[1,2-*a*]pyrido[2,3-*d*]pyrimidin-5-ones is reported from the reaction of 2-aminobenzimidazole with 2-haloaroyl chlorides. The reaction takes advantage of the 1,3-disposition of nucleophilic centers in 2-aminobenzimidazole and the similar arrangement of electrophilic sites in the acid chloride to assemble the central six-membered ring. Initial treatment of 2-aminobenzimidazole (1.2 equiv) with the acid chloride (1 equiv) in the presence of $NaHCO_3$ (2 equiv) in DMF at −10 °C gives acylation at the saturated benzimidazole nitrogen. Subsequent heating to 75 °C, in the same reaction vessel, then completes the synthesis via an S_NAr ring closure by the C2 amino group. The reaction has broad scope, and gives 76–98% yields for the two-step sequence. The final products exist in a tautomeric equilibrium, which can be blocked by acylation at N6.

Benzimidazoles and quinazolinones are important structural units found in biologically active compounds. Numerous derivatives of these structures are found individually in drugs used to treat a wide variety of medical conditions.[1] Commercial benzimidazole-based drugs are used as antihelmintics, antiulceratives, and antihistimines. Quinazolinones also possess beneficial pharmacological properties and are in use or under investigation as anticancer, antiviral, antimicrobial, antihypertensive, anti-inflammatory, and analgesic agents.

Fused-ring structures incorporating the benzimidazole and quinazolinone systems have also been prepared and investigated (Fig. 1). An early report disclosed that benzo[4,5]imidazo[2,1-*b*]-quinazolin-12(5*H*)-one (**1**) exhibited potent immunosuppressive activity.[2] Additionally, derivatives of **1** as well as benzo[4,5]imidazo[1,2-*a*]quinazolin-5(7*H*)-one (**2**) are readily intercalated into DNA, and thus, may exhibit antiproliferative activity in human tumor cell lines.[2,3] Finally, in addition to their potential as anticancer agents, independent studies have also investigated these planar heteroaromatic systems as electron transport and emitter materials.[4]

To date, syntheses of polycyclic aromatic structures related to **1** have been reported using three different strategies. One approach employed an acylation–S_NAr sequence between 2-halo-[5] or 2-sulfo-[6] substituted benzimidazoles and anthranilic acid derivatives. A second synthesis involved the condensation of methyl 2-isothiocyanatobenzoate esters with *o*-phenylenediamine.[3b] Two related reports outlined a third entry to these systems via a copper-catalyzed Ullman coupling of 2-bromobenzoic acid and 1-alkyl-2-aminobenzimidazoles[3a] and a similarly promoted domino reaction between a 2-bromo-*N*-(2-halophenyl)benzamide and cyanamide.[7] Synthetic routes to compounds having the framework found in **2** have also been reported. Two articles documented a sequence involving acylation of 2-aminobenzimidazole with 2-haloaryloyl chlorides, followed in a separate step, by cyclization in boiling pyridine or diphenyl ether (20–78%).[8] Two additional disclosures utilized a copper-mediated coupling reaction: one joined 2-aminobenzimidazole with 2-bromobenzoic acid in refluxing DMF (93%),[9] and the other promoted displacement of halogen from *N*-alkyl-2-halobenzamides by N1 of benzimidazole under anaerobic conditions in DMSO at 120 °C, and then, upon exposure to air at this same temperature, gave oxidative amidation at C2 of the benzimidazole to close the ring (54–98%).[10] The acylation–S_NAr approaches to **1** and **2** described relatively few examples, and thus, the reaction scope for these two methods was limited. Those catalyzed by copper, showed broader applicability, but likely yielded products containing metal impurities, which would require removal prior to use as a drug.

Our strategy was based on two earlier projects in our laboratory[11] and involved a one-pot acylation–S_NAr sequence that

* Corresponding author. Tel.: +1 405 744 5952; fax: +1 405 744 6007.
E-mail address: rab@okstate.edu (R.A. Bunce).

http://dx.doi.org/10.1016/j.tetlet.2015.11.041
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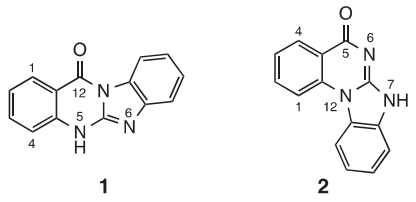
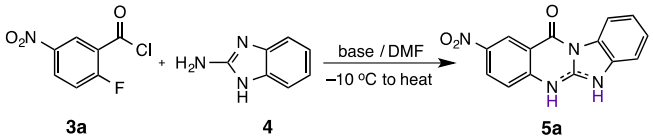


Figure 1. Benzo[4,5]imidazo[2,1-*b*]quinazolin-12(5*H*)-one (**1**) and benzo[4,5]imidazo[1,2-*a*]quinazolin-5(7*H*)-one (**2**) antitumor compounds.

exploited the 1,3-disposed nucleophilic centers in 2-aminobenzimidazole with the similarly positioned electrophilic sites in a 2-haloaroyl chloride to generate the central six-membered ring. Interestingly, two regioisomeric products were possible from the current reaction, one derived from initial acylation of the amino substituent on the benzimidazole to give structures related to **2** and the other from acylation at the saturated benzimidazole nitrogen[8a,12] to give regioisomers similar to **1**. We anticipated that treatment of 2-fluoro-5-nitrobenzoyl chloride (**3a**) with 2-aminobenzimidazole (**4**) in the presence of base would proceed by a sequence involving acylation of the amino function of **4** followed by an S_NAr ring closure to give substituted derivatives of **2**. In practice, however, product **5a**, with the ring system found in **1**, was produced. Using *N*,*N*-dimethylformamide (DMF) as the solvent,[11b] **3a** and **4** were mixed in the presence of different bases at −10 °C, and then heated. When complete, the reaction was worked up and purified to give the yields of **5a** shown in Table 1. Organic bases (TEA, pyridine, and DIPEA) in DMF at 140 °C failed to give acceptable conversions, but sodium and potassium carbonate as well as the corresponding bicarbonates were found to promote complete conversion at 140 °C within 1 h. Since sodium bicarbonate is mild as well as inexpensive, we sought to optimize the temperature using this base. Variation of this parameter revealed that the reaction proceeded at temperatures as low as 75 °C, but slowed dramatically at 45 °C and 60 °C. Thus, our optimized procedure involved treating 2-aminobenzimidazole (1.2 equiv) with the acid chloride (1.0 equiv) in the presence of $NaHCO_3$ (2 equiv) in DMF at −10 °C for 30 min, followed by heating to 75 °C for 0.5–1 h.

Application of these conditions to substrates **3a**–**h** furnished high yields of the target heterocycles **5a**–**h**, allowing slightly broader reaction scope with respect to substitution on the acid chloride than our previous synthesis of pyrazoloquinazolinones.[11b]

Table 1
Reaction optmization



3a **4** **5a**

Entry	Base (2 equiv)	Temp (°C)	Time (h)	Yield (%)[a]
1	TEA	140	12.0	15
2	Pyridine	140	12.0	18
3	DIPEA	140	12.0	26
4	K_2CO_3	140	0.5	88
5	Na_2CO_3	140	1.0	88
6	$KHCO_3$	140	1.0	88
7	$NaHCO_3$	140	1.0	88
8[b]	$NaHCO_3$	75	1.0	88
9	$NaHCO_3$	60	5.0	53
10	$NaHCO_3$	45	5.0	38

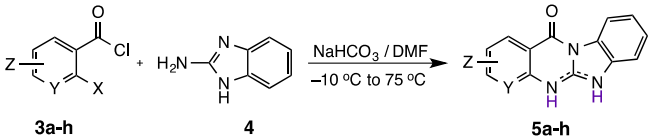
[a] Isolated yields.
[b] Optimized conditions.

Most reactions proceeded at 75 °C, while 2,3,4,5,6-pentafluorobenzoyl chloride (**3e**) gave a near quantitative yield of **5e** after 1 h at 23 °C (Table 2). The reaction workup involved removal of DMF under vacuum, dilution with distilled water, and filtration. The resulting solid was then stirred with ethanol at reflux, cooled, and filtered. While the benzimidazoquinazolinone product did not dissolve significantly in hot ethanol, soluble impurities were removed by this treatment. The low solubility of the products in common organic solvents rendered chromatographic purification ineffective as a means of purification. Poor mass balances were obtained when this was attempted.

In order to broaden the scope of the reaction, we prepared 2-amino-5,6-dimethylbenzimidazole (**6**) from 4,5-dimethylbenzene-1,2-diamine and cyanogen bromide according to a literature procedure.[13] Reaction of **3a**–**g** with **6** using our standard protocol generated the corresponding 8.9-dimethylbenzimidazoquinazolinones **7a**–**g** in high yields. Similarly, nicotinoyl chloride (**3h**) afforded 8,9-dimethylbenzimidazopyridopyrimidin-5-one **7h** (Table 3). Again, the perfluorinated acid chloride afforded excellent conversion to the acylation–S_NAr product at 23 °C.

Previous syntheses of N5- or N6-alkylated benzo[4.5]imidazo-[2,1-*b*]quinazolin-12-ones were reported with unambiguous characterization data,[10] though most of these papers did not report ^{13}C NMR spectra. As the current compounds are not substituted at either of these sites, spectral interpretation proved considerably more difficult. While the ^1H NMR spectra were reasonably sharp, it was observed that many of the absorptions in the ^{13}C NMR spectra were broadened to a point where they could not be observed. It is interesting to note that benzimidazoles normally exist as tautomeric structures having partial double bond character between C2–N1 and C2–N3,[14] with H exchanged between the two nitrogens. We have observed broadened ^{13}C NMR signals resulting from this phenomenon in a previous synthesis of these compounds.[15] In the current systems, tautomerization involved a proton shift between N6 in the benzimidazole moiety and N5 exocyclic to the benzimidazole; due to its tertiary structure and electron-deficient substitution, N11 was not involved in this tautomerization. The NH proton was often not observed in the ^1H NMR, presumably due to H-bonding with the solvent, which would shift the signal well beyond the normal chemical shift range.[16] The broadened signals in the ^{13}C NMR spectra for the current products clearly indicated that the bonding situation in these materials was not straightforward. Earlier studies failed to report ^{13}C NMR spectra, which is understandable since our attempts to acquire these data were hampered by the tautomeric nature and low solubility of the

Table 2
Cyclizations to form products **5a**–**h**

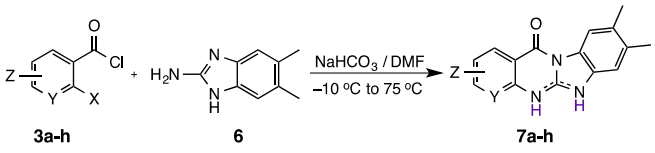


3a-h **4** **5a-h**

Substrate	X	Y	Z	Pdt	Z	Yield (%)[a]
3a	F	CH	5-NO_2	**5a**	2-NO_2	88
3b	F	CH	H	**5b**	H	87
3c	F	CH	5-F	**5c**	2-F	86
3d	F	CH	6-F	**5d**	1-F	93
3e	F	CF	4,5,6-F	**5e**	1,2,3-F	96[b]
3f	F	CH	4-Me	**5f**	3-Me	76
3g	F	CH	4-Br	**5g**	3-Br	78
3h	Cl	N	H	**5h**	H	90

[a] Isolated yields.
[b] Reaction was complete in 1 h at 23 °C.

Table 3
Cyclizations to form products **7a–h**



3a-h **6** **7a-h**

Substrate	X	Y	Z	Pdt	Z	Yield (%)[a]
3a	F	CH	5-NO_2	**7a**	2-NO_2	91
3b	F	CH	H	**7b**	H	83
3c	F	CH	5-F	**7c**	2-F	87
3d	F	CH	6-F	**7d**	1-F	95
3e	F	CF	4,5,6-F	**7e**	1,2,3-F	98[b]
3f	F	CH	4-Me	**7f**	3-Me	80
3g	F	CH	4-Br	**7g**	3-Br	84
3h	Cl	N	H	**7h**	H	95

[a] Isolated yields.
[b] Reaction was complete in 1 h at 23 °C.

compounds (even at 110 °C in DMSO-d_6). In particular, the aromatic carbons for most of the products as well as the methyl carbons of **7a–h** were broadened significantly, particularly for **5a**,**d**,**f** and for **7b**,**c**,**d**,**f**. Resolution of this problem was accomplished by treatment of these products with acetyl chloride and triethylamine, which selectively acylated N6 as illustrated below (Table 4). An X-ray structure of 6-acetyl-2-nitrobenzo[4,5]imidazo[2,1-*b*]quinazolin-12(6*H*)-one (**8a**), derived from **5a** (Fig. 2) confirmed the site of reaction. Most of the acylated derivatives showed improved solubility and gave sharp peaks in the ^{13}C NMR spectrum at 75 °C in DMSO-d_6. However, the acetamides of **7c** and **7f** also proved to be highly insoluble, and thus, the hexanoyl derivatives were prepared. The hexanamides presented no solubility problems and the spectra were readily acquired in $CDCl_3$ at 23 °C. As an added benefit, these derivatization experiments revealed a facile method for modulating the solubility of these compounds.

Interestingly, some structures did not show significant signal broadening in the ^{13}C NMR. This was noted in products derived from acid chlorides **3e** and **3h**, which incorporated electron deficient fused tetrafluorobenzo (**7e** and **8e**) and pyrido (**7h** and **8h**) moieties. These derivatives gave sharp signals in their ^{13}C NMR spectra. A possible explanation for this observation is that the electron-deficient ring draws the double bond away from the benzimidazole making tautomerization less important. Furthermore, positioning of the conjugated double bond in the six-membered

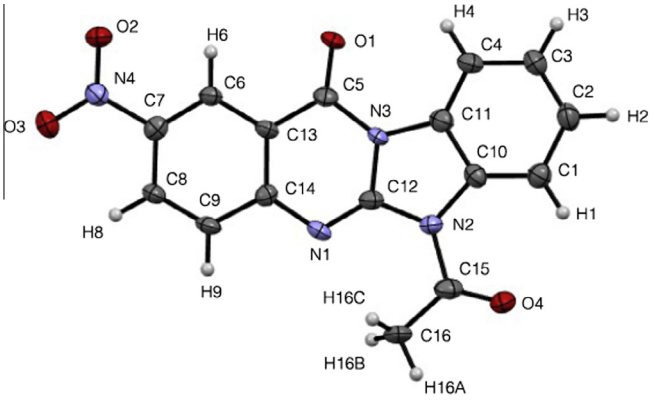


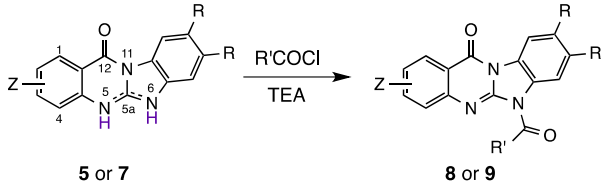
Figure 2. X-ray structure of **8a** (CCDC 1424687).

ring *exo* to the five-membered imidazole ring should also be favorable. Other structures derived from acid chlorides bearing only one electron-withdrawing group (e.g., **3a**, **3c**, and **3d**) were not sufficiently electron deficient, to elicit this effect.

The presumed mechanism to convert **3a** and **4** to **5a** is depicted in Fig. 3. Since bicarbonate is an insufficiently strong base to deprotonate 2-aminobenzimidazole (**4**, pK_a ca. 16),[17] it serves to scavenge protons after the various addition–elimination processes take place. Following acylation of **4** at N1 by **3a**, bicarbonate would deprotonate intermediate **9** to give amide **10**. At this stage, the amino nitrogen would attack the fluorinated carbon initiating an S_NAr addition–elimination to give **11**. Final deprotonation by the second equivalent of base, would then afford benzimidazoquinazolinone **5a** as a mixture of tautomers.

In conclusion, we have developed a one-pot sequential procedure to prepare benzo[4,5]imidazo[1,2-*a*]quinazolin-12-ones and benzo[4.5]imidazo[1,2-*a*]pyrido[2,3-*d*]pyrimidin-5-ones using an acylation–S_NAr sequence. The strategy involves the reaction between the 1,3-disposed nucleophilic centers in 2-aminobenimidazole and the similarly arranged electrophilic sites in the 2-haloaroyl chlorides to construct the central six-membered ring of the fused heterocyclic targets. The products are formed in high yields by a procedure that eliminates high temperatures, strong bases, and metal catalysts. The ^{13}C NMR spectra of the products exhibit broad signals, which suggest that the structures are tautomeric across the N5–C5a–N6 triad. Acylation of these products results in exclusive reaction at N6. This locks the double bond into the six-membered ring and improves solubility, making NMR

Table 4
Acylation of N6 to block tautomerization



5 or 7 **8 or 9**

Substrate	Z	R	R′	Pdt	Yield (%)[a]
5a	2-NO_2	H	Me	**8a**	94
5d	2-F	H	Me	**8d**	96
5f	3-Me	H	Me	**8f**	92
7b	H	Me	Me	**9b**	88
7c	2-F	Me	Hex	**9c**	85
7d	1-F	Me	Me	**9d**	93
7f	3-Me	Me	Hex	**9f**	97

[a] Isolated yields.

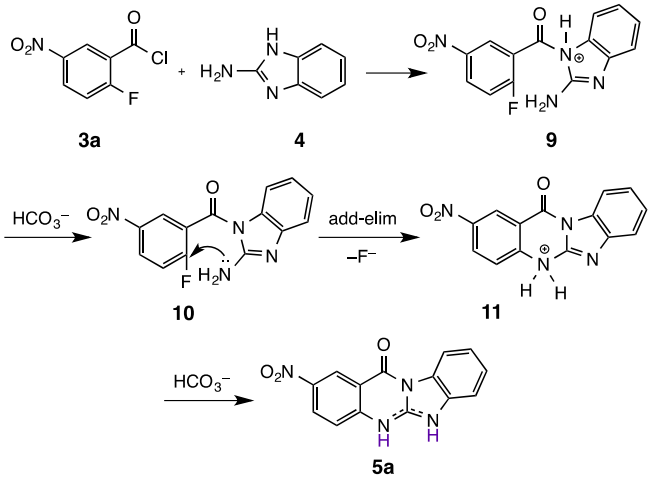


Figure 3. Presumed mechanism for the reaction of **3a** and **4** to give **5a**.

characterization more straightforward. A presumed mechanism is presented to account for the observed transformation.

Acknowledgments

NSF (BIR-9512269), the Oklahoma State Regents for Higher Education, the W.M. Keck Foundation and Conoco, Inc. provided funds to establish the Oklahoma State-wide NMR Facility. The Oklahoma State University College of Arts and Sciences is also acknowledged for providing funds to purchase a new 400 MHz NMR for this facility and to maintain our FT-IR and mass spectrometer instruments. NSF (CHE-0130835) and the University of Oklahoma provided funds to purchase the X-ray instrument and computers at the University of Oklahoma Chemical Crystallography Laboratory. Finally, the authors wish to thank Dr. Margaret Eastman and Dr. Dongtao Cui for assistance with the high temperature NMR experiments and Dr. Douglas Powell for obtaining the X-ray crystal structure.

Supplementary data

Supplementary data (experimental details, spectral characterization for compounds **5a–h**, **7a–h, 8a**, **8d**, **8f**, **9b–d** and **9f** and X-ray crystallographic tables for **8a** (CCDC 1424687)) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.11.041.

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