Imidoyl dichlorides as new reagents for the rapid formation of 2-aminobenzimidazoles and related azoles

Julie A. Pollock, Sung Hoon Kim, John A. Katzenellenbogen

PII: S0040-4039(15)30118-0
DOI: http://dx.doi.org/10.1016/j.tetlet.2015.09.076
Reference: TETL 46748

To appear in: *Tetrahedron Letters*

Received Date: 29 August 2015
Accepted Date: 17 September 2015

Please cite this article as: Pollock, J.A., Kim, S.H., Katzenellenbogen, J.A., Imidoyl dichlorides as new reagents for the rapid formation of 2-aminobenzimidazoles and related azoles, *Tetrahedron Letters* (2015), doi: http://dx.doi.org/10.1016/j.tetlet.2015.09.076

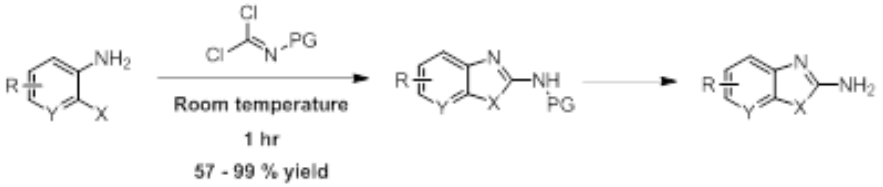
Graphical Abstract

To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

Imidoyl dichlorides as new reagents for the rapid formation of 2-aminobenzimidazoles and related azoles

Leave this area blank for abstract info.

Julie A. Pollock*†, Sung Hoon Kim, and John A. Katzenellenbogen



ELSEVIER

Tetrahedron Letters
journal homepage: www.elsevier.com

Imidoyl dichlorides as new reagents for the rapid formation of 2-aminobenzimidazoles and related azoles

Julie A. Pollock*†, Sung Hoon Kim, and John A. Katzenellenbogen

Department of Chemistry, University of Illinois at Urbana–Champaign, Urbana, Illinois 61801, United States

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
2-aminobenzimidazole
Imidoyl dichloride
Azole synthesis
PhIP
Benzimidazole

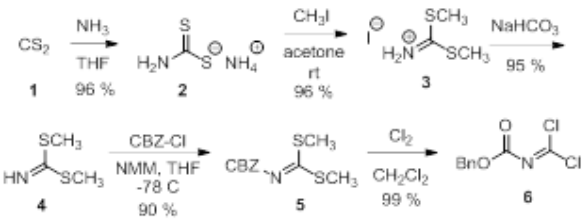
ABSTRACT

The development of a reagent for the efficient synthesis of 5- and 6-membered azoles at room temperature is proposed. A variety of substituted 2-aminobenzimidazoles are synthesized in good to excellent yields. The ability to incorporate various protecting groups makes the imidoyl dichloride reagent amenable to a large number of syntheses. The reagent is applied to the total synthesis of the 2-aminobenzimidazole containing carcinogen, 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP), from 2-chloro-3-nitropyridine in >60 % yield in 6 steps.

1. Introduction

The 2-aminobenzimidazole core is an integral component of many compounds having interesting biological activity. This core is found in antagonists against glucagon receptor,[1] G9a histone methyltransferase,[2] IL-1 receptor-associated kinase-4,[3] inducible T-cell kinase,[4] and H3-receptor.[5] Additionally, drugs with this core have shown antimicrobial and antifungal activity including inhibition of the growth of gram-negative bacteria and inhibition of biofilm formation.[6] Furthermore, 2-aminobenzimidazoles have been reported to have antiproliferative and cytotoxic activity against a variety of cancer cells.[7] Because of the diverse biological functions of this class of compounds, a synthetic route that is applicable to multiple substrates, easy to perform and high yielding would facilitate exploration of the immense opportunities for useful bioactivity that is afforded by this core.

Common methods for generating 2-aminobenzimidazoles include cyclization of *o*-phenylenediamines with cyanogen bromide, reaction of 2-chlorobenzimidazoles with amines at high temperatures, activation of *o*-phenylenediamine as a thiourea followed by cyclization and desulfurization using mercury(II) oxide, or reflux of an aryl isothiocyanate with a *o*-phenylenediamine using a carbodiimide reagent.[8] However, because of high temperatures, long reaction times and/or low yields involved in these methods, a rapid and efficient production of 2-aminobenzimidazoles amenable to a variety of functionality is desired.



Scheme 1. Synthesis of CBZ-protected imidoyl dichloride, **6**.

2. Results and Discussion

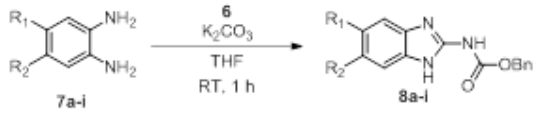
We were inspired by a paper[9] utilizing a carbonimidodithioic ester reagent that selectively reacted with anilines in the presence of a free carboxylic acid. However, the reaction necessitated heating in DMF at 150 °C for 9h. We hypothesized that replacement of the thioethers with chlorides would allow for a more rapid reaction, perhaps even at room temperature. The reagent, carboxybenzyl protected imidoyl dichloride (**6**), was synthesized (Scheme 1) beginning with carbon disulfide and ammonia. The thioethers were installed by reaction with methyl iodide, and the CBZ-protecting group was easily attached under normal conditions. Lastly, the thioethers were substituted using chlorine condensed in CCl_4. **6** is an

* Corresponding author. Tel.: 1-804-484-1578; fax: 1-804-287-1897; email: jpollock@richmond.edu

† Present address. Department of Chemistry, University of Richmond, Richmond, VA 23173, United States

oil that is stable for months in the freezer. The reaction of **6** with 1,2-phenylenediamine proceeded mildly within 1 hr at room temperature in either tetrahydrofuran or dichloromethane with potassium carbonate as the base (Table 1, entry 1). The use of triethylamine resulted in longer reaction times and produced impurities as identified by ^{1}H NMR of the crude product (data not shown).

Table 1. Scope of reaction with aryldiamines.[a]



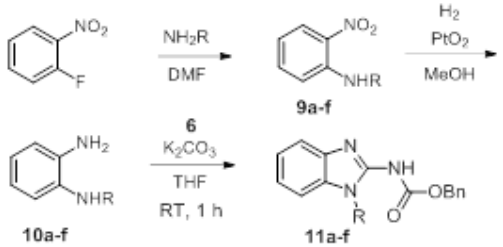
entry	R_1	R_2	product	Yield (%)
1[b]	H	H	**8a**	75
2	Br	H	**8b**	76
3	F	H	**8c**	71
4	Cl	H	**8d**	78
5	Cl	Cl	**8e**	97
6	CN	H	**8f**	70
7	OCH_3	H	**8g**	70
8	NO_2	H	**8h**	81
9	CO_2H	H	**8i**	70

[a] Reaction conditions: **7** (0.1 mmol) and K_2CO_3 (0.25 mmol) were suspended in THF (1 mL). **6** (0.12 mmol) in THF (1 mL) was added and the reaction stirred for 1 hr at RT.

[b] Reaction performed on 1 mmol scale.

We tested the scope of our reagent by reacting **6** with a variety of commercially available *o*-phenylenediamines (Table 1, entries 2-9) for 1 hr at room temperature with potassium carbonate in tetrahydrofuran. Each reaction proceeded in good to excellent yield under mild conditions. The reaction is tolerant of electron-releasing (entry 7) and electron-withdrawing groups (entries 2, 3, 4, 5, 6, 8) substituents. Of note, only the 2-aminobenzimidazole was formed even in the presence of a free carboxylic acid (entry 9).

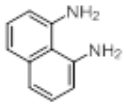
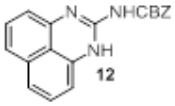
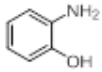
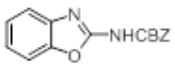
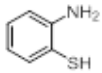
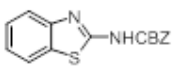
Table 2. Scope of reaction with substituted *o*-phenylenediamines.



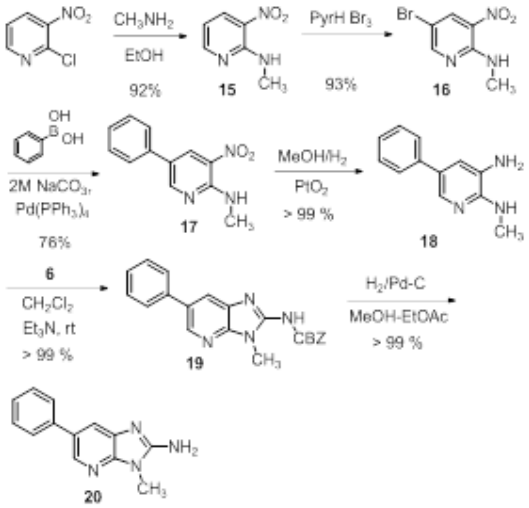
entry	R	Yield **9** (%)	Yield **10** (%)	Yield **11** (%)
a	Ethyl	72	98	89
b	*n*-Propyl	85	99	93
c	*n*-Butyl	85	99	73
d	*t*-Butyl	98	98	70
e	Benzyl	85	99	97
f	Phenyl	98	99	70

Next, we expanded the screen to include N^1-substituted 1,2-phenylenediamines (Table 2). These were synthesized by a traditional sequence starting from 1-fluoro-2-nitrobenzene. The nucleophilic aromatic substitution proceeded in good to excellent yields to produce **9a-f** and reduction of the nitro group to **10a-f** through hydrogenation using platinum oxide was essentially quantitative. When these compounds were subjected to **6** at room temperature for 1 hr, the reaction proceeded very well (**11a-f**). Even with more sterically hindered substituents like *t*-butyl and phenyl (**11d**, **11f**, respectively) the reaction proceeded in good yield.

Table 3. Scope of reaction with alternative scaffolds.

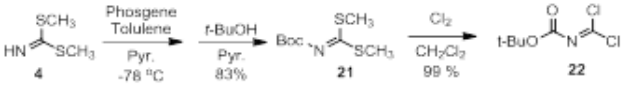
entry	sm	product	Yield (%)
1		 **12**	78
2		 **13**	85
3		 **14**	65

We investigated the synthetic utility of our new reagent by expanding the scope of the starting material. As illustrated in Table 3, the reaction with 1,8-diaminonaphthalene (entry 1, **12**) proceeded in a good yield within 1 hr at room temperature. When 2-aminophenol (entry 2, **13**) or 2-aminothiophenol (entry 3, **14**) were used, the reaction proceeded favorably to produce the corresponding benzoxazole and benzothiazole, respectively.



Scheme 2. Synthesis of PhIP.

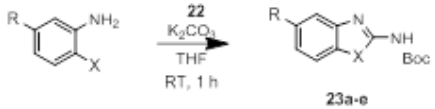
2-Amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP, **20**) is a known carcinogen produced amino acid condensations during high temperature cooking of meat and fish.[10] Previous syntheses of **20** have required steps at high temperatures and proceeding in low yields.[11] We applied our CBZ-protected imidoyl dichloride reagent **6** as the penultimate step (Scheme 2) and were able to produce **20** from the inexpensive 2-chloro-3-nitropyridine in >60 % yield over 6 steps.



Scheme 3. Synthesis of Boc-protected Imidoyl Dichloride, **22**.

Initially, we chose a carboxybenzyl protecting group for our imidoyl dichloride reagent for ease of monitoring the reactions by TLC and removal by hydrogenation. However, we predicted the chemistry could be amenable to additional protecting groups. Indeed, we were able to prepare a *t*-butyloxycarbonyl protected imidoyl dichloride (**22**) through reaction of the S,S'-dimethyliminiothiocarbonate (**4**) with phosgene followed by *t*-butanol and finally the displacement of the thioethers with chlorine. Similar to **6**, reaction of **22** with 1,2-phenylenediamines afforded the 2-aminobenzimidazoles (Table 4) rapidly and in good yields regardless of the electronic nature of the ring substituents (entries b-c) and the *N*-substitution (entry d). In addition, reaction of **22** with 2-aminophenol afforded the corresponding benzoxazole in good yield (entry e). We predict that the imidoyl dichoride reagents would be amenable, as well, to alternative amine protecting groups, allowing for the rapid production of 2-aminobenzimidazoles and related azoles that could be further derivatized as desired.

Table 4. Scope of reaction with **22**.



23a-e

entry	R	X	Yield (%)
a	H	NH	81
b	OCH_3	NH	70
c	NO_2	NH	93
d	H	$N(CH_2CH_2CH_3)$	88
e	H	O	57

3. Conclusions

Overall, we have developed a robust reagent tolerant of multiple functional groups that allows for the rapid formation of benzimidazole or alternative azole rings at room temperature.

Supplementary Material

Supplementary data (experimental procedures and spectral data for all new compounds) associated with this article can be found in the online version.

Acknowledgments

Research support is granted from the National Institutes of Health (PHS 5R37DK015556 to J.A.K). J.A.P. was supported by training fellowship from the National Institutes of Health (T32ES007326).

References and notes

1. Kim, R. M.; Chang, J.; Lins, A. R.; Brady, E.; Candelore, M. R.; Dallas-Yang, Q.; Ding, V.; Dragovic, J.; Iliff, S.; Jiang, G. Q.; Mock, S.; Qureshi, S.; Saperstein, R.; Szalkowski, D.; Tamvakopoulos, C.; Tota, L.; Wright, M.; Yang, X. D.; Tata, J. R.; Chapman, K.; Zhang, B. B.; Parmee, E. R. *Bioorg. Med. Chem. Lett*. **2008,** *18,* 3701.
2. Kubicek, S.; O'Sullivan, R. J.; August, E. M.; Hickey, E. R.; Zhang, Q.; Teodoro, Miguel L.; Rea, S.; Mechtler, K.; Kowalski, J. A.; Homon, C. A.; Kelly, T. A.; Jenuwein, T. *Mol. Cell* **2007,** *25,* 473.
3. Powers, J. P.; Li, S.; Jaen, J. C.; Liu, J.; Walker, N. P. C.; Wang, Z.; Wesche, H. *Bioorg. Med. Chem. Lett.* **2006,** *16,* 2842.
4. (a) Moriarty, K. J.; Takahashi, H.; Pullen, S. S.; Khine, H. H.; Sallati, R. H.; Raymond, E. L.; Woska, J. R.; Jeanfavre, D. D.; Roth, G. P.; Winters, M. P.; Qiao, L.; Ryan, D.; DesJarlais, R.; Robinson, D.; Wilson, M.; Bobko, M.; Cook, B. N.; Lo, H. Y.; Nemoto, P. A.; Kashem, M. A.; Wolak, J. P.; White, A.; Magolda, R. L.; Tomczuk, B. *Bioorg. Med. Chem. Lett.* **2008,** *18,* 5545. (b) Winters, M. P.; Robinson, D. J.; Khine, H. H.; Pullen, S. S.; Woska, J. R.; Raymond, E. L.; Sellati, R.; Cywin, C. L.; Snow, R. J.; Kashem, M. A.; Wolak, J. P.; King, J.; Kaplita, P. V.; Liu, L. H.; Farrell, T. M.; DesJarlais, R.; Roth, G. P.; Takahashi, H.; Moriarty, K. J. *Bioorg. Med. Chem. Lett.* **2008,** *18,* 5541.
5. Rivara, M.; Zuliani, V.; Cocconcelli, G.; Morini, G.; Comini, M.; Rivara, S.; Mor, M.; Bordi, F.; Barocelli, E.; Ballabeni, V.; Bertoni, S.; Plazzi, P. V. *Bioorg. Med. Chem.* **2006,** *14,* 1413.
6. (a) Kus, C.; Goker, H.; Altanlar, N. *Arch. Pharm.* **2001,** *334,* 361. (b) Taher, A. T.; Khalil, N. A.; Ahmed, E. M.; Ragab, Y. M. *Chem. Pharm. Bull*. **2012,** *60,* 778. (c) Rogers, S.A.; Huigens, R.W.; Melander, C. *J. Am. Chem. Soc.* **2009,** *131,* 9868. (d) Frei, R.; Breitbach, A. S.; Blackwell, H. E. *Angew. Chem. Int. Ed.* **2012,** *51,* 5226.
7. Nawrocka, W.; Sztuba, B.; Kowalska, M. W.; Liszkiewicz, H.; Wietrzyk, J.; Nasulewicz, A.; Pełczyńska, M.; Opolski, A. *Il. Farmaco.* **2004,** *59,* 83.
8. (a) Turteltaub, K. W.; Knize, M. G.; Healy, S. K.; Tucker, J. D.; Felton, J. S. *Fd. Chem. Toxic.* **1989,** *27,* 667. (b) Perkins, J. J.; Zartman, A. E.; Meissner, R. S. *Tet. Lett.* **1999,** *40,* 1103. (c) Carpenter, R. D.; Deberdt, P. B.; Lam, K. S.; Kurth, M. J. *J. Comb. Chem.* **2006,** *8,* 907-914.
9. Lee, J. H.; An, M. H.; Choi, E. H.; Choo, H. Y. P.; Han, G. *Heterocycles* **2006,** *70,* 571.
10. (a) Felton, J. S.; Knize, M. G.; Shen, N. H.; Lewis, P. R.; Andresen, B. D.; Happe, J.; Hatch, F. T. *Carcinogenesis,* **1986,** *7,* 1081. (b) Felton, J. S.; Knize, M. G.; Shen, N. H.; Lewis, P. R.; Andresen, B. D.; Bjeldanes, L. F.; Hatch, F. T. *Environ. Health Perspect.* **1986,** *67,* 17.
11. (a) Knize, M. G.; Felton, J. S. Heterocycles 1986, 24, 1815. (b) Choshi, T.; Tonari, A.; Yoshioka, H.; Harada, K.; Sugino, E.; Hibino, S. *J. Org. Chem.* **1993,** *58,* 7952. (c) Nguyen, T.M.; Novak, M. *J. Org. Chem.* **2007,** *72,* 4698. (d) Chrisman, W.; Knize, M. G.; Tanga, M. J. *J. Heterocycl. Chem.* **2008,** *45,* 1641.