Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 47 (2006) 8079–8081

# Convenient synthesis of *N*-(4-(2-aminopyridin-4-yl)thiazol-2-yl)-2-phenylacetamides

Upul K. Bandarage,* Jon H. Come and Jeremy Green

*Vertex Pharmaceuticals Incorporated, 130, Waverley Street, Cambridge, MA 02139, United States*

Received 17 August 2006; revised 8 September 2006; accepted 12 September 2006
Available online 4 October 2006

**Abstract**—We report a facile one-pot, three-step synthesis of *N*-(4-(2-aminopyridin-4-yl)thiazol-2-yl)-2-phenylacetamides via condensation of 2-*p*-methoxybenzylamino-4-acetylpyridine with phenylacetylthioureas.
Published by Elsevier Ltd.

As a part of our medicinal chemistry research program, we were interested in synthesizing *N*-(4-(2-aminopyridin-4-yl)thiazol-2-yl)-2-phenylacetamides **1**. The synthesis of this class of compounds has not been previously reported to our knowledge. The most straightforward synthetic approach to introduce an amino group at the 2-position of pyridine is by thermal or microwave assisted reaction of benzylamines with 2-chloro or 2-fluoropyridines **2** to afford **3**,[1] or by transition metal assisted coupling of 2-halopyridines with benzyl amines or ammonia equivalents[2] (Fig. 1). These methods failed in our hands despite attempts under various reaction conditions.

An alternative approach involves the Hantzsch reaction between a phenylacetylthiourea and an appropriate 2-benzylamino-4-(2-bromoacetyl)pyridine. This reaction has been utilized successfully to form the analogous *N*-(4-(3-aminophenyl)thiazol-2-yl)acetamides starting from 3-nitroacetophenone.[3] However we could not apply this transformation directly to the pyridine systems as the required starting material, 2-nitro-4-acetylpyridine, is not commercially available nor easily accessed synthetically. Therefore, we modified the reaction sequence, and below we report our successful efforts to prepare *N*-(4-(2-aminopyridin-4-yl)thiazol-2-yl)-2-phenylacetamides in a one-pot procedure using a modification of this route.

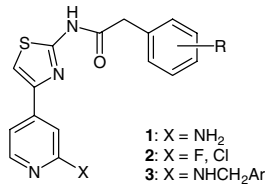
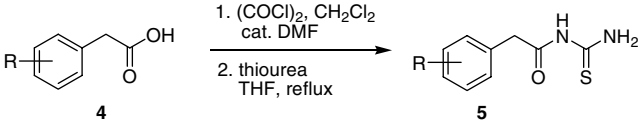



**Figure 1.** Thiazolyl pyridines.

Phenylacetylthioureas **5** could be readily synthesized from commercially available phenylacetic acids **4**, which were first converted to acid chlorides with oxalyl chloride and then reacted with excess thiourea to give phenylacetylthioureas **5** in 30–50% yield[4] (Scheme 1).

The synthesis of the other condensation partner, 2-*p*-methoxybenzylamino-4-(2-bromoacetyl)pyridine **6**, is outlined in Scheme 2. The reaction of 2-fluoro-4-cyanopyridine **7**[5] with *p*-methoxybenzylamine in DMA at 130 °C gave **8** in high yield. Compound **8** was subsequently converted to the 4-acetylpyridine **9** in good yield by treatment with methyl magnesium bromide.

The reaction of **9** with bromine in a mixture of 48% aqueous HBr and acetic acid at 70 °C over 30 min gave



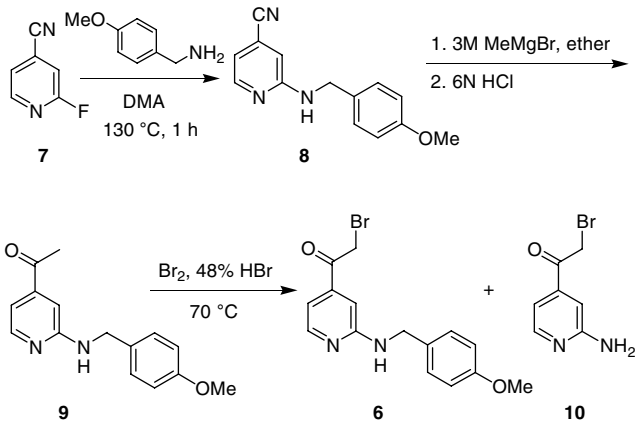

**4** **5**

**Scheme 1.** Synthesis of monoacylated thiourea.

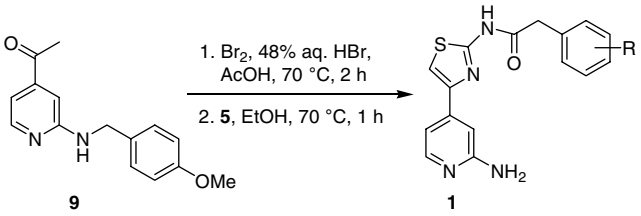
*Keywords*: 2-Aminopyridine; Thiourea; Thiazole; Bromination; α-Bromoketone.

* Corresponding author. Tel.: +1 617 444 6882; fax: +1 617 444 7827; e-mail: upul_bandarage@vrtx.com

0040-4039/$ - see front matter Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2006.09.053




**Scheme 2.** Synthesis of 2-*p*-methoxybenzylamino-4-(2-bromoacetyl)-pyridine **6**.



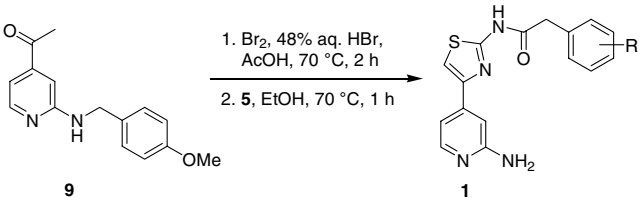

**Scheme 3.** Preparation of *N*-(4-(2-aminopyridin-4-yl)thiazol-2-yl)-2-phenylacetamides.

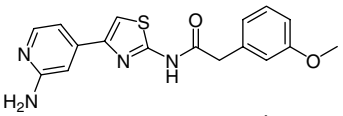
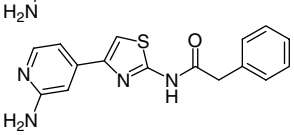
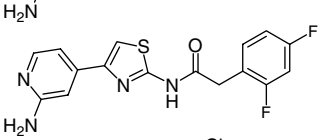
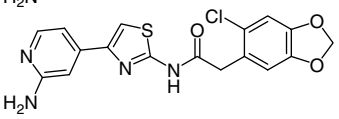
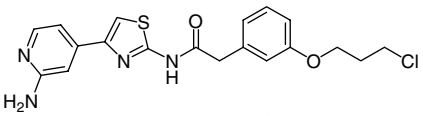
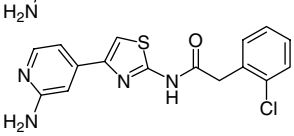
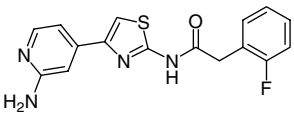
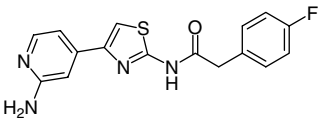
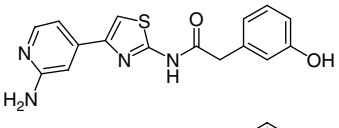
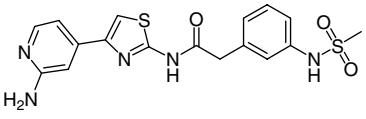
a mixture of the desired α-bromoketone **6** as well as the debenzylated 2-amino-4-(2-bromoacetyl)pyridine **10**. Heating the reaction mixture for a longer period of time (2 h) at 70 °C, resulted in the formation of **10** exclusively (Scheme 2).

The isolation of **10** proved problematic due to its high water solubility. Therefore, generation of **10** in situ, followed by reaction with **5** was next considered. Upon completion of α-bromination and cleavage of the *p*-methoxybenzyl (PMB) group, the resulting **10** was directly reacted with an ethanolic solution of **5** to afford the target molecule, **1** (Scheme 3). This one-pot, three-step transformation was employed to produce a variety of substituted *N*-(4-(2-aminopyridin-4-yl)thiazol-2-yl)-2-phenylacetamides in moderate yields after chromatography[6] (Scheme 3). The results of the reactions between various phenylacetylthioureas **5** and **9** are summarized in Table 1.

In conclusion, we have developed an efficient one-pot, three-step synthesis of *N*-(4-(2-aminopyridin-4-yl)thiazol-2-yl)-2-phenylacetamides from readily available starting materials in moderate yield. This method is particularly useful for the selective preparation of *N*-acylaminothiazoles in the presence of an aminopyridine group in the same molecule and therefore, provides easy access for the variation of acylated thiazole moiety for structure activity relationship studies in medicinal chemistry research.

**Table 1.** Formation of *N*-(4-(2-aminopyridin-4-yl)thiazol-2-yl)-2-phenylacetamides




| Entry | Product | Yield |
|---|---|---|
| 1 |  | 56 |
| 2 |  | 46 |
| 3 |  | 52 |
| 4 |  | 36 |
| 5 |  | 38 |
| 6 |  | 43 |
| 7 |  | 48 |
| 8 |  | 52 |
| 9 |  | 28 |
| 10 |  | 48 |

## Acknowledgments

The authors wish to acknowledge Dr. Robert Perni and Joe Drumm at Vertex Pharmaceuticals for valuable comments and suggestions.

## References and notes

1. Usui, S.; Suzuki, T.; Hattori, Y.; Etoh, K.; Fujieda, H.; Nishizuka, M.; Imagawa, M.; Nakagawa, H.; Kohda, K.; Miyata, N. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1547–1551.

2. (a) Lee, S.; Jorgensen, M.; Hartwig, J. F. *Org. Lett.* **2001**, *3*, 2729–2732; (b) Hartwig, J. F. In *Modern Amination Methods*; Ricci, A., Ed.; Wiley-VCH: Weinheim, 2000; (c) Wolfe, J. P.; Wagaw, S.; Marcoux, J. F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805–818.
3. (a) Kawamatsu, Y.; Sohda, T.; Imai, Y. *Eur J. Med. Chem. Chim. Ther.* **1981**, *16*, 355–362; (b) Ohkubo, M.; Kuno, A.; Nakanishi, I.; Takasugi, H. *Chem. Pharm. Bull.* **1995**, *43*, 1497–1504.
4. General procedure for the preparation of phenylacetylthiourea. A solution of oxalyl chloride in $CH_2Cl_2$ (2 M, 4.5 mL, 9 mmol) was added to a stirred solution of *m*-methoxyphenylacetic acid (1.0 g, 6.02 mmol) in DMF (0.1 mL) and $CH_2Cl_2$ (25 mL) and the resulting clear solution was stirred at ambient temperature for 1 h. The solvent was removed under reduced pressure and the acid chloride residue was dissolved in THF (25 mL), and thiourea (1.82 g, 24 mmol) was added. The mixture was refluxed for 6 h and cooled to room temperature. The solution was poured into water (100 mL) and extracted with EtOAc ($3 \times 50$ mL). The organic extracts were dried over $Na_2SO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (hexanes–EtOAc) to give *N*-(3-methoxyphenylacetyl)-thiourea **5** (0.48 g, 35%) as a white solid. $^1$H NMR (500 MHz, DMSO-$d_6$) 11.23 (s, 1H), 9.55 (br s, 1H), 9.36 (br s, 1H), 7.23 (dd, $J = 7.9$ Hz, 1H), 6.82–6.87 (m, 3H), 3.73 (s, 3H), 3.66 (s, 2H); Electrospray MS: $m/z = 225$ ($MH^+$).
5. Frey, L. F.; Marcantonio, K.; Frantz, D. E.; Murry, J. A.; Tillyer, R. D.; Grabowski, E. J. J.; Reider, P. J. *Tetrahedron Lett.* **2001**, *42*, 6815–6818.
6. General procedure for the preparation of *N*-(4-(2-aminopyridin-4-yl)thiazol-2-yl)-2-phenylacetamides. Bromine (0.01 mL, 0.195 mmol) was added to a stirred solution of 2-*p*-methoxybenzylamino-4-acetylpyridine **9** (0.05 g, 0.195 mmol) in 48% aqueous HBr (0.2 mL) and AcOH (0.4 mL), and the solution was heated at 70 °C for 2 h. A solution of *N*-(3-methoxyphenylacetyl)-thiourea **5** (0.044 g, 0.195 mmol) in ethanol (3 mL) was then added and the heating was continued for 1 h. The solution was poured into water (10 mL) and made basic by the addition of concentrated $NH_4OH$ and the product was extracted with EtOAc ($3 \times 10$ mL). The crude product was purified by preparative HPLC (column: Kromasil C8 $21.2 \times 150$ mm; 20 mL/min; gradient 10–90% MeCN (0.1% TFA) in $H_2O$ (0.1% TFA) over 15 min) to give **1** (Table 1, entry 1) (56%). $^1$H NMR (500 MHz, DMSO-$d_6$) 12.6 (br s, 1H), 7.93 (d, 1H), 7.86 (s, 1H), 7.24 (t, 1H), 7.09 (s, 2H), 6.83–6.93 (m, 5H), 3.77 (s, 2H), 3.73 (s, 3H); Electrospray MS: $m/z = 341$ ($MH^+$).