# Thermal Synthesis of 3-Bromothieno[3,2-*c*]pyridin-4-(5*H*)-one: A Telescoped Procedure with Tributylamine

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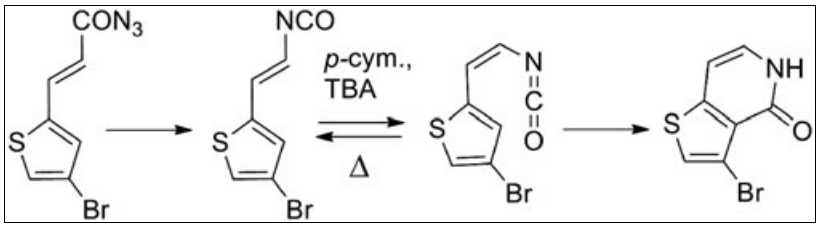
Received July 18, 2012
DOI 10.1002/jhet.1981
Published online 00 Month 2014 in Wiley Online Library (wileyonlinelibrary.com).




3-Bromothieno[3,2-*c*]pyridine-4-(5*H*)-one (**1**) was prepared from (2*E*)-3-(4-bromo-2-thienyl)-2-propenoic acid (**3**) by the Eloy–Deryckere thermal benzo/heteropyridinone synthesis. A telescoped procedure was developed, which reduces some of the risk associated with the classic procedure. Use of tributylamine as an additive in this process was shown to facilitate *E*/*Z*-isomerization of the intermediate vinyl isocyanate and lower the temperature necessary for the overall thermal process.

*J. Heterocyclic Chem.*, **00,** 00 (2014).

## INTRODUCTION

3-Bromothieno[3,2-*c*]pyridine-4-(5*H*)-one (**1**) is widely employed as an intermediate for synthesis of medicinally relevant 3-aryl-4-aminothieno[3,2-c]pyridines of general structure **2** (Scheme 1), including potassium channel blockers [1] and kinase inhibitors [2–4]. Recently, two new routes to **1** were described [5], including both Friedel–Crafts and reductive cyclization protocols. Even so, the classic "thermal" synthesis of Eloy and Deryckere [6] continues to be applied [7,8] for the preparation of benzopyridinones (and thienopyridinones) owing to procedural ease (for small scale) and inexpensive starting materials.

We recently performed a laboratory scale-up of **1** for use as an intermediate to support kinase inhibitor lead optimization programs in our laboratories. In the course of this work, we developed a simple procedure that mitigates some of the risks associated with the thermal route. In addition, some insight was gained into the role of tributylamine as an additive in this process. The details of this study are described herein.

## RESULTS AND DISCUSSION

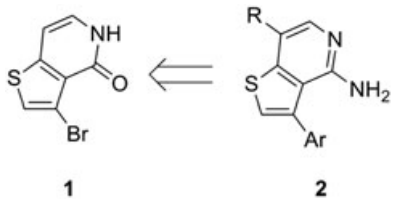
The reaction path for the thermal route [9] (Scheme 2) involves conversion of the thiophene acrylic acid **3** to acyl azide **4** [10] followed by Curtius degradation to the vinyl isocyanate *E*-**5**. Double-bond isomerization of *E*-**5** to *Z*-**5** sets up a 6π electrocyclization to afford hydropyridinone intermediate **6**, which undergoes a sigmatropic hydrogen shift to yield the desired product (**1**). The temperatures generally reported for the alkene isomerization and electrocyclization sequence in Scheme 2 (*E*-**5** → **6**) are very high (e.g. 220–240°C). In fact, compound **1** may degrade under such forcing reaction conditions [5].

Catalysis studies with mercuric acetate suggest that alkene isomerization is the rate-limiting step [9] in this pathway. In fact, both iodine [11,12] and mercuric acetate [9] can reduce temperatures by about 50–60°C for this process (e.g. 170–180°C). Addition of tributylamine as an additive is also known to increase yields of cyclized product [13] but at temperatures similar to those reported for the non-catalyzed process [2,6,13]. To our knowledge, the exact role of tributylamine in this process is not described, although we assumed it facilitates alkene isomerization (*E* → *Z*) of the isocyanate intermediate (**5**).

Use of tributylamine as an additive was intriguing to us, owing to its moderate reactivity, low toxicity, and high boiling point (214–216°C). This article reports on the results of our investigations into the role of tributylamine in this process. In addition, we describe a telescoped procedure for converting carboxylic acid **3** to thienopyridinone **1** that alleviates some of the safety concerns associated with the synthesis.

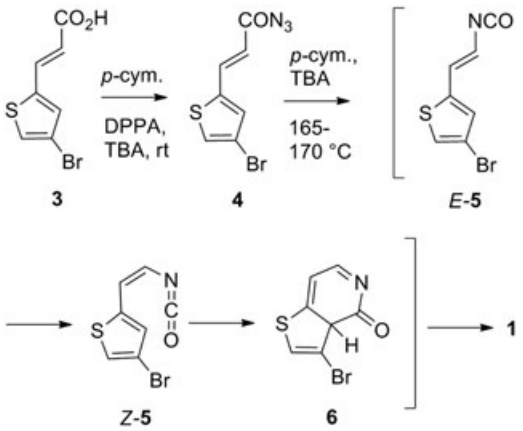
We originally prepared acyl azide **4** by published methods [3]. Preliminary stability studies with **4** showed that decomposition (by Curtius degradation) began at 75–80°C; for this reason, multi-gram operations with this material were performed in solution at RT. Two NMR sample solutions of **4** (~0.05 *M*) in $d_4$-1,2-dichlorobenzene were prepared. Both samples were heated in the same 100°C oil bath for 30 min, which effected complete conversion to *E*-**5**. One of the NMR samples containing *E*-**5** was subsequently treated with tributylamine (~2 equiv), and both samples were re-heated at 100°C for an additional 30 min. The NMR

**Scheme 1**




1 2

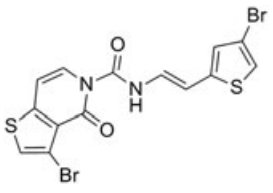
**Scheme 2**




3 4 *E*-5 *Z*-5 6

spectrum of the sample containing tributylamine [Fig. 1(A)] showed a new pair of AB-doublets consistent with ~50% isomerization to *Z*-**5** (δ 5.85 and 5.83 ppm, $J = 7.4$ Hz). Heating this sample for an additional 90 min at 147°C effected conversion to **1** [Fig. 1(B)].

Conversely, after 30 min at 100°C, the NMR spectra of the sample without tributylamine added showed only the AB pattern of vinylic doublets corresponding to *E*-**5** [Fig. 1(C): δ 6.15 and 6.10 ppm, $J = 13$ Hz]. Heating this sample for an additional 90 min at 147°C produced minimal changes in the spectrum [Fig. 1(D)], although a very small multiplet at δ 5.84 ppm corresponding to *Z*-**5** was observed. Additional resonances also appeared, which we assigned to carbamoyl thienopyridinone **7** (in analogy to a previously described benzopyridinone syntheses [9,13]). Heating the sample without tributylamine for 60 min at 180°C completed the cyclization to **1**.

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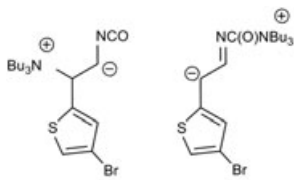
Two possible pathways for tributylamine-mediated *E*/*Z*-isomerization of **5** involve reversible Michael [14] or isocyanate [15] addition-elimination pathways, which would yield zwitterionic intermediates **8** and **9**, respectively. Rotation of the requisite carbon–carbon bond in these intermediates, followed by elimination of tributylamine, would effect interconverion of *E*-**5** and *Z*-**5**. Assuming alkene isomerization is rate-limiting in the absence of additive, tributylamine effectively facilitates electrocyclization at a lower temperature (similar to mercuric acetate catalysis [9]). A change in mechanism for hydrogen migration is also plausible (from a 1,5-shift to a 1,3-shift) under tributylamine base catalysis [16].

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A modified procedure for conversion of **3–1** was subsequently devised. We chose *p*-cymene as solvent owing to its high bp (177°C), low density (relative to water), and low freezing point relative to diphenyl ether (the most common solvent employed for this process). The desired compound (**1**) also crystallizes from hot *p*-cymene on cooling [17].

Telescoping the title synthesis simply entailed generating the acyl azide from the carboxylic acid with diphenylphosphoryl azide and tributylamine in *p*-cymene at RT. This stage was performed on a 1.29-mol scale of **3** in a 6-L fixed glass jacketed lab reactor. Following acyl azide formation, multiple washing with NaOH (1.0 *M*) removed the diphenylphosphoric acid by-product, without detriment to the acyl azide, and avoided solvent exchange and charging of tributylamine prior to the critical high temperature stage. The organic phase containing **4** and tributylamine was separated, dried, filtered, and split into two separate batches (~0.64 mol each) for further processing.

Metered addition of the *p*-cymene solution of **4** and tributylamine to neat *p*-cymene at 165–170°C was performed over 3 h. Azide addition by pump from a relatively remote position (as opposed to an overhead dropping funnel) minimized risk of accidental spillage over the hot reaction vessel. This reverse addition at temperatures well above that required for Curtius degredation, alkene isomerization, and electrocyclization enabled control of both reactive inventory (acyl azide) and nitrogen production. To ensure complete reaction, the mixture was stirred for 2.5 h at 170°C following the addition.

Our results support the supposition that tributylamine facilitates vinyl isocyanate isomerization in the Eloy–Deryckere (benzo/hetero)pyridinone synthesis and in turn enables electrocyclization at lower temperature. Moreover, telescoping the acyl azide and thienopyridinone syntheses

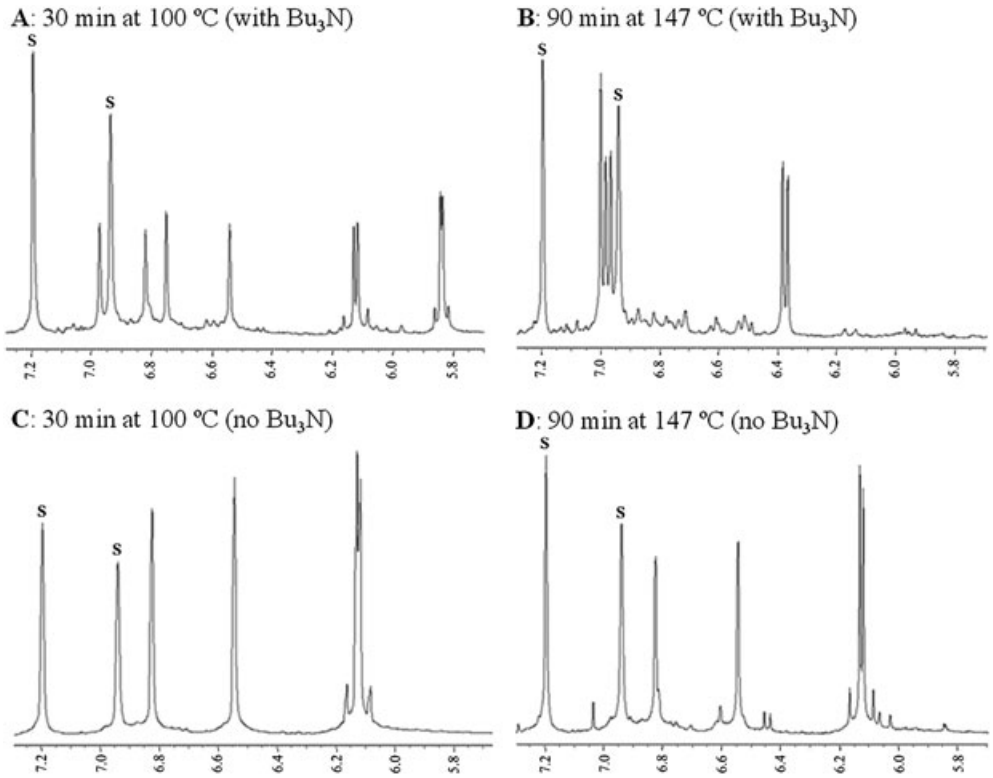


**Figure 1.** $^1$H NMR spectra (400 MHz; 7.2–5.8 ppm) from solutions isocyanate *E*-5 *in* $d_4$-dichlorobenzene after heating with (A and B) and without (C and D) tributylamine. Solvent peaks (S) are labeled (7.20 and 6.94 ppm).

with tributylamine in *p*-cymene avoids both isolation of azide **4** and charging of tributyl amine prior to the high temperature stage. The modified procedure affords the title compound in good yield (71%) and purity (>98% by LCMS). Spectral data of **1** were in agreement with literature values [5].

## EXPERIMENTAL

**3-Bromo-thieno[3,2-*c*]pyridin-4-(5*H*)-one (1).** Diphenyl phosphorylazide (390 g, 1.42 mol) was added drop wise to a stirred solution of (2*E*)-3-(4-bromo-2-thienyl)-2-propenoic acid (300 g, 1.29 mol) and tributylamine (286 g, 1.54 mol) in *p*-cymene (2.2 L) at RT, and the reaction mixture was stirred overnight. The reaction mixture was basified with 1N NaOH. The phases were separated, and the organic layer was washed with 1N NaOH (2 × 2 L) to remove the diphenylphosphoric acid by-product. The organic phase was washed with brine, dried over $MgSO_4$, and filtered. The *p*-cymene filtrate containing **4** and tributylamine was split into two equal volumes and used in separate batches without further purification. This solution (0.64 mol of **4**) was added by pump over 3 h (flow rate 8 mL/min) to stirred *p*-cymene (2 L) at 165°C internal temperature. Following the addition, the reaction mixture was maintained at 170°C for an additional 2.5 h and then allowed to cool to ambient temperature overnight. The slurry was diluted with heptane (700 mL), cooled to −10°C, and the product (**1**) was collected by filtration as a light beige solid (105 g, 71% yield): LCMS purity >98%; *m*/*z* 230 (M + 1), 232 (M + 1); $^1$H NMR (400 MHz, DMSO-$d_6$) δ 6.83 (d, 1H, J = 7 Hz), 7.24 (d, 1H, J = 7 Hz), 7.63 (br s, 1H), 11.46 (br s, 1H) [5].

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