A Convenient Preparation of Thieno[3,2-c]pyrazole

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Abstract: A practical synthesis of multigram quantities of 1H-thieno[3,2-c]pyrazole is presented in which the Jacobson reaction serves as the key step.

Key words: aminations, cyclizations, polycycles, heterocycles

Pyrazoles are an important class of biomolecules. Biologically active pyrazoles include lonazolac, apixaban, crizotinib, and rutolitinib. Condensed pyrazoles such as 1H-indazole (1) have become important pharmaceutical scaffolds. Less well known are thienopyrazoles, such as 1H-thieno[3,2-c]pyrazole (2) and 1H-thieno[2,3-c]pyrazole (3). It is known that thiophene is an acceptable bioisostere for benzene and, therefore, thienopyrazoles 2 and 3 should serve as substitutes for indazole (Figure 1).

Figure 1 Condensed pyrazoles

To support studies related to the synthesis of potential kinase inhibitors, we needed large quantities of thieno[3,2-c]pyrazole (2). Two syntheses of 2 have been reported by Gronowitz and co-workers (Scheme 1). The first synthesis started from 3-bromothiophene-2-carbaldehyde (4), which was subjected to aromatic nucleophilic substitution with sodium azide to give azide 5 in 48% yield. Treatment of azide 5 with hydrazine hydrate in boiling ethanol containing a small amount of acetic acid gave the desired thieno[3,2-c]pyrazole (2). In the second method, also starting from azide 5, the azide group was reduced to amine 6, which was then diazotized. Reduction of the resulting diazonium salt 7 gave thieno[3,2-c]pyrazole (2). Thus, 2 was available in a 7.7% overall yield by a two-step sequence or in a 5.7–12% yield through a four-step sequence. These syntheses are unsatisfactory for preparing the larger amounts of 2 required for preparation of analogues of the compound. Here, we describe our efforts to develop a more efficient route to 1H-thieno[3,2-c]pyrazole (2).

A possible route to 2, which we discarded, involved reduction of the nitro imine 8 by triethyl phosphite to give the 2-arylthieno[3,2-c]pyrazole 9 (Scheme 2). We felt that this route suffered from difficulties in obtaining the starting material and from the need to remove the N2 substituent. Cyclizations of azo compounds and of diazonium salts are commonly used methods for the synthesis of condensed pyrazoles such as indazole. A variant on this is the Jacobson reaction. This reaction converts ortho-methyl amines into pyrazoles through N-acetylation, nitration, and cyclization, and may proceed via the diazonium salt. To apply this reaction to the synthesis of 1H-thieno[3,2-c]pyrazole, we needed sufficient quantities of 2-methylthiophene-3-amine (11). This amine, in turn, should be obtainable from commercially available methyl 3-aminothiophene-2-carboxylate (10).

We knew that anthranilic acid (12) gives o-toluidine (13) on reduction with aluminum hydride, so we initially used this procedure to reduce ester 10. However, the preparation of aluminum hydride was always a daunting task, so we sought a more expedient reduction and we noted that use of lithium aluminum hydride in refluxing 1,4-dioxane had been reported to reduce the ethoxycar-
bonyl group in esters 14 directly to the methyl group in carbazoles 15 (Scheme 3).\(^\text{17}\)

![Scheme 3 Reagents and conditions: (a) AlH₃, Et₂O; (b) LAH, 1,4-dioxane, reflux.](image)

We found that when a solution of ester 10 was added slowly to a suspension of lithium aluminum hydride in refluxing 1,4-dioxane, subsequent workup gave crude (2-methyl-3-thienyl)amine (11), which was then used directly in the cyclization step (Scheme 4). Note that when all the reactants were mixed together at room temperature and then heated, a vigorous off-gassing occurred at 80 °C, with concomitant frothing, usually out of the flask. The reduction was uneventful, however, when the addition was performed at 70 °C. Subsequently, we found that the reaction can also be carried out in refluxing tetrahydrofuran. The use of this latter solvent avoids the difficulties encountered in removing 1,4-dioxane, namely the freezing of the solvent in the condenser and distillation of some product.

Cyclization of 11 was effected simply by acetylation of the amine group in toluene in the presence of potassium acetate, followed by treatment of the resulting mixture with isoamyl nitrite and heating for several hours. The N-acetate 16 was readily purified by column chromatography and trituration with pentane to remove a foul-smelling impurity. The acetyl group was removed by acetylation, as reported in the literature\(^\text{1 or, more conveniently, by saponification with potassium hydroxide. The overall yield of this three-step sequence to unsubstituted thieno[3,2-c]pyrazole (2) was 47%.}

During the chromatographic purification of product 16, a more polar material was isolated and identified as the acetylated dimer 22. The simplest way to account for the formation of this byproduct is to assume that the starting material underwent amidation to form dimer 19 during the reduction process or that dimer 19 was present as an impurity in the starting material. Reduction of 19 to diamine 20 and subsequent processing during the Jacobson reaction would account for the formation of byproduct 22 (Scheme 5).

In a completely different approach, we were able to prepare thieno[3,2-c]pyrazole (2) by means of a palladium-catalyzed cyclization reaction (Scheme 6). 3-Bromothiophene-2-carbaldehyde (23) was prepared by the method of Iddon and co-workers.\(^\text{18}\) Condensation of this material with benzophenone hydrazone (27) gave azine 24. Palladium-catalyzed addition of hydrazone 27 to azine 24 gave the bishydrazone 25, which was hydrolyzed with concentrated hydrochloric acid to give thieno[3,2-c]pyrazole (2) via the hydrazine aldehyde 26. The overall yield of this four-step process from commercially available 3-bromothiophene was 40.4%; however, the poor atom economy (74% of the mass of 27 is lost in the cyclization step) and the estimated higher cost per gram of the final product persuaded us to favor the Jacobson reaction.

![Scheme 4 Reagents and conditions: (a) LAH, 1,4-dioxane, 70–101 °C; (b) KOAc, Ac₂O, toluene, r.t. to 46 °C then Me₂CH(CH₂)₂ONO, 80–104 °C, 4–6 h, 52% yield (from 10); (c) KOH, EtOH, 90% yield.](image)

![Scheme 5 Proposed route to the dimeric byproduct](image)
In conclusion, by using the Jacobson reaction, we developed a practical three-step process for the preparation of large (30–50 g) quantities of 1H-thiено[3,2-c]pyrazole (2) in reasonable yield starting from a commercially available material. We also prepared 2 through palladium-catalyzed amination of thiophene as the key step.

Melting points were determined with a Thomas–Hoover capillary melting point apparatus and are uncorrected. TLC analyses were performed with Merck DC-F254 silica gel plates, with visualization by UV irradiation. Flash chromatography was performed with Fisher 200–245 mesh chromatographic silica gel or by using ISCO RediSep silica gel cartridges. NMR spectra were recorded in CDCl₃, unless otherwise stated, on a Varian Mercury-300 spectrometer operated at 300 MHz for ¹H NMR and at 75.4 MHz for ¹³C NMR; signals are reported in ppm relative to TMS. Mass spectral data were collected on a Micromass Platform LCZ or Micromass LCT spectrometer by using the electrospray ionization technique. The organic extracts were dried over MgSO₄ or Na₂SO₄ before dropwise over 1 h, with caution, to a mechanically stirred suspension, allowed to warm to r.t. and then refluxed overnight. The cooled wash were concentrated to afford a brown liquid [¹H NMR: δ = 2.22 (s, 3 H), 3.32 (br s, 2 H), 6.56 (d, 1 H), 6.89 (d, 1 H)] that evaporated under vacuum in a rotary evaporator.

Reagents and conditions: (a) Ph₃P=NNH₂ (27), EtOH, 70 °C, 30 h; 85% yield; (b) Ph₃P=NNH₂ (27), Pd(OAc)₂, Cs₂CO₃, 1,1'-bis(diphenylphosphino)ferrocene (dpff), toluene, 100 °C, 24 h; (c) coned HCl, EtOH, 56% yield (2 steps).

1-Acetyl-1H-thiено[3,2-c]pyrazole (16)
Amine 11 was dissolved in toluene (600 mL) and the solution was treated with KOAc (34.37 g, 350 mmol). The vigorously stirred mixture was treated by dropwise addition of Ac₂O (97.6 mL, 864.9 mmol) over about 20 min. The temperature rose rapidly from 23 to 46 °C during the first half of the addition.¹⁹ The flask containing the mixture was then placed in an oil bath heated to 80 °C. When the reaction temperature reached 75 °C, isoamyl nitrite (66.7 mL, 496.4 mmol) was added dropwise over 30 min. The temperature rose slowly to 104 °C. After 4 h, heating was discontinued and the reaction mixture was stirred overnight at r.t. The solids were removed by filtration and washed with toluene (3 × 200 mL). The organic phases were concentrated and recombined to form a black liquid from which crystals deposited on standing. The mixture was dissolved in a small amount of CH₂Cl₂, diluted with heptane–10% EtOAc and purified in by flash chromatography [silica gel (7.2 × 25 cm), heptane–10% EtOAc (1:7)]. Then heptane–15% EtOAc (4 L). The fractions (500 mL each) containing the pure product were combined and concentrated to afford a yellow solid [38.55 g (62%)] that was stirred with pentane (300 mL) for 4 h, then collected by filtration, washed with pentane (2 × 100 mL), and dried to give a light-beige solid,²⁰ yield: 32.53 g (52%).

²¹H NMR (300 MHz, CDCl₃): δ = 2.75 (s, 3 H), 7.58 (s, 2 H), 7.90 (s, 1 H).

²¹C NMR (75.4 MHz, CDCl₃): δ = 12.43, 21.32, 23.48, 113.52, 122.06, 126.27, 134.06, 135.88, 144.45, 147.42, 168.34, 170.78.

Scheme 6   Alternative synthesis of 1H-thiено[3,2-c]pyrazole (2).
concentrated. The resulting solid was crystallized (EtOAc) to give tan needles; yield: 14.1 g (90%).

1H NMR (300 MHz, CDCl3): δ = 7.02 (d, 1 H), 7.41 (d, 1 H), 7.79, (s, 1 H), 10.0–10.6 (br s, 1 H).

1H NMR (75.4 MHz, DMSO-d6): δ = 7.07 (d, 1 H), 7.56 (d, 1 H), 7.71 + 8.00 (s + s, 0.6 H + 0.4 H), 12.98 + 13.30 (br s + br s, 0.6 H + 0.4 H). This spectrum showed that 2 exists as a mixture of the N1-H and N2-H tautomers in a ratio of 3:2.

LC/MS (ESI): m/z = 125.02.


Base Hydrolysis: A solution of 1-acetylthieno[3,2-c]pyrazole (16, 9.75 g, 58.66 mmol) in MeOH (100 mL) was treated with KOH (5.66 g, 100 mmol) and the mixture was heated at 80 °C for 24 h, then cooled to r.t. The solids were removed by filtration and the solvent was evaporated to give the crude hydrazine (25 g); total yield: 29.3 g (85%).

(1Z)-1-[3-(Bromo-2-thienyl)methylene]-2-(diphenylmethyl)hydrazine (24)
A mixture of 3-bromo-2-thiophenecarboxaldehyde (23; 29.3 g, 153 mmol) and benzophenone hydrazone (26; 33.1 g, 168 mmol) in EtOH (200 mL) was stirred at 70 °C for 5 h. The mixture was cooled to r.t. and the solids were collected by filtration to give a yellow solid (12.9 g); yield: 46.7 g (82%). Crystallization (EtOAc-heptane) gave beige needles; yield: 6.58 g (90%); mp 156–158 °C.

1H NMR (300 MHz, CDCl3): δ = 8.71 (d, J = 5.4 Hz, 1 H), 7.75 (s, 1 H), 7.77 (br s, 1 H), 12.99 (br s, 1 H).

LC/MS (ESI): m/z = 125. MS (ESI): m/z = 125 [M + 1].

- Thieno[3,2-c]pyrazole (2) from Hydrazine 25
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