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

John Airey, Matthieu Barrague, Michael L. Edwards, Michael Ferro, Dirk Friedrich, Timothy A. Gillespy, John Jurcak, Kwon Musick, Philip M. Weintraub

Sanofi-Aventis, 1041 Route 202-206, P.O. Box 6800, Bridgewater, NJ 08807-0800, USA
E-mail: philipmweintraub@gmail.com

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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 3-bromothiophene-2-carbaldehyde (4), which was then diazotized. Reduction of the resulting diazonium salt gave 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).

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).

Scheme 1 Previous synthesis of 1H-thieno[3,2-c]pyrazole. Reagents and conditions: (a) NaN₃, DMSO, 65 °C, 48 h, 48% yield; (b) N₂H₄·H₂O, AcOH, EtOH, 16% yield; (c) H₂S, EtOH; (d) NaNO₂, HCl; (e) Na₂S₂O₄, 12–25% yield (3 steps).

A possible route to 2, which we discarded, involved reduction of the nitro imine 8 by triethyl phosphite to give the 2-aryltieno[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 orthomethyl amines into pyrazoles through N-acetylation, nitrosation, 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).

Scheme 2 Discarded route to 1H-thieno[3,2-c]pyrazole. Reagents and conditions: (a) (EtO)₃P, t-BuPh.

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).17

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 acid hydrolysis, as reported in the literature1 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.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.
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-thieno[3,2-c]pyrazole (2).

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. Mass spectral data were collected on a Micromass Platform LCZ or Micromass Q-TOF spectrometer by UV irradiation. Flash chromatography was performed with Merck DC-F254 silica gel plates, with visualization by UV irradiation. 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.

Alternative synthesis of 1H-thieno[3,2-c]pyrazole (2)

**Reagents and conditions:** (a) Ph$_3$C=NNH$_2$ (27), EtOH, 70 °C, 30 h; 85% yield; (b) Ph$_3$C=NNH$_2$ (27), Pd(OAc)$_2$, Cs$_2$CO$_3$, 1,1′-bis(diphenylphosphino)ferrocene (dppf), toluene, 100 °C, 24 h; (c) concd HCl, EtOH, 56% yield (2 steps).

**Scheme 6** Alternative synthesis of 1H-thieno[3,2-c]pyrazole (2). Reagents and conditions: (a) Ph$_3$C=NNH$_2$, EtOH, 70 °C, 30 h; 85% yield; (b) Ph$_3$C=NNH$_2$, Pd(OAc)$_2$, Cs$_2$CO$_3$, 1,1′-bis(diphenylphosphino)ferrocene (dppf), toluene, 100 °C, 24 h; (c) concd HCl, EtOH, 56% yield (2 steps).

1-Acetyl-1H-thieno[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 Ac$_2$O (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. The flask containing the mixture was then placed in an oil bath heated to 80 °C. When the reaction temperature reached 75 °C, isomyl 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 combined to form a brown liquid (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 (yield: 32.53 g (52%).

## Acid Hydrolysis

1H NMR (300 MHz, CDCl$_3$): δ = 2.75 (s, 3 H), 7.58 (s, 2 H), 7.90 (s, 1 H).

13C NMR (75.4 MHz, CDCl$_3$): δ = 21.75, 113.78, 128.84, 134.25, 135.28, 147.36, 188.81.

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Analysis. Caled for C$_{14}$H$_{13}$N$_3$O$_2$: C, 52.64; H 4.10; N, 13.16; S, 20.08. Found: C, 52.92; H, 3.92; N, 13.26; S, 20.08.

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concentrated. The resulting solid was crystallized (EtOAc) to give ten needles; yield: 14.1 g (90%).

$^1$H NMR (300 MHz, CDCl$_3$): $\delta = 7.02$ (d, 1 H), 7.41 (d, 1 H), 7.79, (s, 1 H), 10.0–10.6 (br s, 1 H).

$^1$H NMR (75 MHz, DMSO-$d_6$): $\delta = 7.07$ (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.


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 (3.29 g, 58.63 mmol) and the mixture was heated at 60 °C for 3 h. The cooled mixture was concentrated, and the residue was partitioned between EtOAc (150 mL) and H$_2$O (150 mL). The separated aqueous layer was extracted with more EtOAc (2 × 100 mL). The organic layers were combined, washed with brine (3 × 250 mL). The organic solution was treated with concd aq HCl (250 mL). The mixture was heated at 80 °C for 3 h then cooled. H$_2$O (1.5 L) and EtOAc (500 mL) were added, followed by Na$_2$CO$_3$ until the pH was neutral. The aqueous layer was separated and extracted with EtOAc (3 × 250 mL). The organic layers were combined, dried, filtered, and concentrated to give a brown oil that was purified by chromatography (silica gel, heptane–10% EtOAc to heptane–40% EtOAc). Product-containing fractions were combined and concentrated to give a pink solid; yield: 9 g (56%).

References


(2) Current address: Retired.

(3) Current address: Chemical Research, Sanofi US, 153 2nd Ave, Waltham, MA 02451, USA.

(4) Current address: 33 Casale Drive South, Warren, NJ 07059, USA.


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