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Short Note

tert-Butyl 3-(4-Cyano-5-phenylisothiazol-3-yl)carbazate

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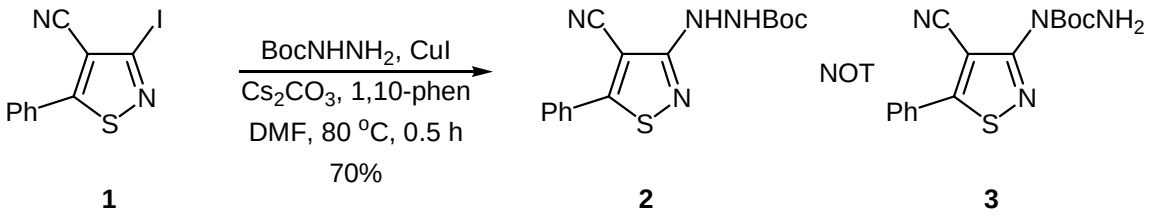
Abstract: 3-Iodo-5-phenylisothiazole-4-carbonitrile **1** reacts with *tert*-butyl carbazate *via* a Buchwald C-N style coupling to afford *tert*-butyl 3-(4-cyano-5-phenylisothiazol-3-yl)-carbazate **2** in 70% yield.

Keywords: isothiazole; hydrazine; Buchwald coupling

We recently attempted to synthesize 3-hydrazinyl-5-phenylisothiazole-4-carbonitrile by reaction of 3-chloro-5-phenylisothiazole-4-carbonitrile with hydrazine, but obtained instead 3-amino-5-phenylpyrazole-4-carbonitrile [1]. A more detailed investigation of this isothiazole to pyrazole transformation, led to the preparation of both 4-bromo-5-phenyl and 4,5-diphenylisothiazol-3-yl-hydrazines by treating the respective 3-haloisothiazoles with anhydrous hydrazine for short durations at elevated temperatures [2]. Despite this success, attempts to prepare the desired 3-hydrazinyl-5-phenylisothiazole-4-carbonitrile were unsuccessful.

An alternative strategy to access 3-hydrazinyl-5-phenylisothiazole-4-carbonitrile involved preparing the title compound *via* modified Buchwald C-N coupling conditions [3–5]. As such, the reaction of 3-iodo-5-phenylisothiazole-4-carbonitrile **1** [1] with *tert*-butyl carbazate in the presence of copper iodide and cesium carbonate as base, together with 1,10-phenanthroline as the ligand, in dry DMF at 80 ^{o}C gave the Boc protected 3-hydrazinyl-5-phenylisothiazole-4-carbonitrile **2**.



1 **2** **3**

Elemental analysis supported an empirical formula of $C_{15}H_{16}N_4O_2S$ and LREI gave a weak parent ion of *m/z* 316 Da (1%) with a major ion at 216 Da (100%) corresponding to the loss of the Boc group. IR spectroscopy supports the presence of the amino [ν(N-H) 3350w & 3239w], cyano [ν(C≡N) 2216w] and the carbonyl [ν(C=O) 1722s] functionalities. Despite this data, two possible isomers could still be formed whereby coupling occurred *via* the carbazate β or α nitrogens to give either isothiazoles **2** or **3**, respectively. ^{1}H NMR spectroscopy, showed two separate NH resonances at δ_H 6.83 and 6.64 ppm that integrated in a ratio of 1:1, tentatively supporting isothiazole **2** to be the correct product. The alternative isomer *tert*-butyl 2-(4-cyano-5-phenylisothiazol-3-yl)carbazate **3** should exhibit a single NH resonance in the ^{1}H NMR spectrum with an integration supporting two hydrogens [3].

Experimental

DMF was azeotropically distilled with PhH then distilled under vacuum from anhydrous $MgSO_4$ and stored over 4 Å molecular sieves. Anhydrous Na_2SO_4 was used for drying organic extracts and volatiles were removed under reduced pressure. The reaction mixture and column eluents were monitored by TLC using commercial glass backed thin layer chromatography (TLC) plates (Merck Kieselgel 60 F_{254}). The plates were observed under UV light at 254 and 365 nm. The technique of dry flash chromatography was used using Merck Silica Gel 60 (less than 0.063 mm). Melting point was determined using a PolyTherm-A, Wagner & Munz, Koefler-Hotstage Microscope apparatus. IR spectrum was recorded on a Shimadzu FTIR-NIR Prestige-21 spectrometer with Pike Miracle Ge ATR accessory and strong, medium and weak peaks are represented by s, m and w respectively. ^{1}H NMR spectrum was recorded on a Bruker Avance 300 machine (at 300 MHz). Deuterated chloroform was used for homonuclear lock and the signals are referenced to the deuterated solvent peak. Low resolution (EI) mass spectrum was recorded on a Shimadzu Q2010 GCMS with direct inlet probe. Microanalysis was performed at London Metropolitan University.

tert-*Butyl 3-(4-cyano-5-phenylisothiazol-3-yl)carbazate* (**2**)

A mixture of 3-iodo-5-phenylisothiazole-4-carbonitrile **1** (100 mg, 0.32 mmol), *tert*-butyl carbazate (2 equiv, 84 mg), CuI (1 equiv, 61 mg), Cs_2CO_3 (1.2 equiv, 125.2 mg), and 1,10-phenanthroline (10 mol%, 6 mg) in anhydrous DMF (4 mL) was stirred at 80 ^oC for 0.5 h. The reaction mixture was allowed to cool to *ca.* 20 ^oC, diluted with water and extracted with DCM (4 × 25 mL). The organic extracts were combined, adsorbed onto silica and chromatographed (hexane/DCM, 3:7) to afford the *title compound* **2** (71 mg, 70%) as a colourless solid, mp 129.2-130.2 ^oC (from cyclohexane); (Found: C, 57.03; H, 5.05; N, 17.67. $C_{15}H_{16}N_4O_2S$ requires C, 56.94; H, 5.10; N, 17.71%); ν_{max}/cm^{-1} 3350w, 3239w, 2972w, 2932w, 2216w (C≡N), 1722s (C=O), 1526m, 1501m, 1481m, 1456w, 1395w, 1369m, 1358m, 1275m, 1254m, 1219m, 1157s, 1067w, 1049w, 1036w, 1001w, 964w, 935w, 880w, 847m, 797m, 770s, 758w, 725w; δ_H (300 MHz, $CDCl_3$) 7.73-7.70 (2H, m, Ph C*H*), 7.53-7.47 (3H, m, Ph C*H*), 6.83 (1H, s, N*H*), 6.64 (1H, s, N*H*), 1.49 (9H, s, CH_3); *m/z* (EI) 316 (M^+, 1%), 260 (35), 242 (16), 216 (M^+ - Boc, 100), 200 (7), 128 (8), 121 (21), 77 (11), 57 (99).

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Sample Availability: Samples of the compounds are available from the corresponding author.