A Short Synthesis of the PARP Inhibitor 2-(4-Trifluoromethylphenyl)benzimidazole-4-carboxamide (NU1077)

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A four-step synthesis of the PARP inhibitor 2-(4-trifluoromethylphenyl)benzimidazole-4-carboxamide (**1**, NU1077) is presented. Condensation of 2,3-diaminotoluene and 4-trifluoromethylbenzaldehyde afforded 4-methyl-2-(4-trifluoromethylphenyl)benzimidazole. Oxidation of the methyl group with potassium permanganate in warm *t*-butanol afforded the carboxylic acid that was converted to the corresponding carboxamide *via* the acid chloride.

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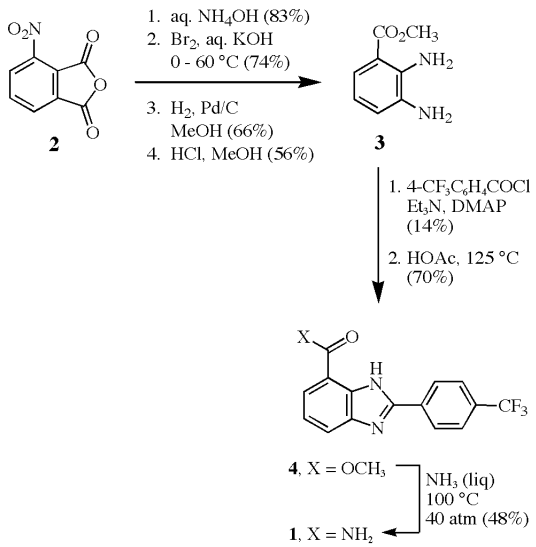
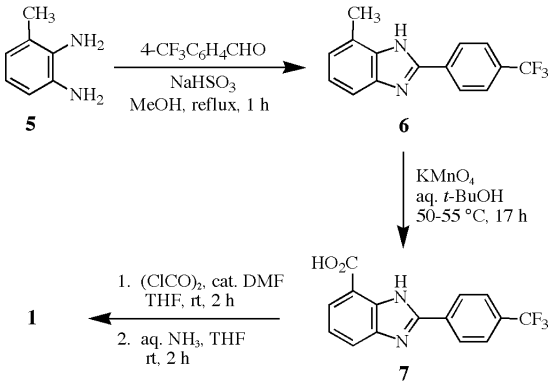
Poly(ADP-ribose)polymerase (PARP: EC 2.4.2.30) is an abundant enzyme found in the nuclei of most eukaryotic cells, where it is thought to play an important physiological role in the repair of DNA strand breaks [1]. Once activated, PARP catalyzes the attachment of ADP-ribose units to nuclear proteins and to itself, in the process consuming four molecules of ATP for each NAD that is regenerated [2]. In disease states where an over activation of PARP is observed, *e.g.*, those involving ischemia-reperfusion, the ensuing massive depletion of NAD^+ and ATP results in necrosis [3]. Thus, inhibitors of PARP have been proposed as agents for the treatment of cerebral [4], myocardial [5], and renal [6] ischemia. It has also been proposed that inhibitors of this enzyme may potentiate the effects of cancer chemo- and radiotherapy [7]. In this regard, selected 2-arylbenzimidazole-4-carboxamides have been reported as potent inhibitors of PARP [7b]. In conjunction with our own studies in this area, we were asked to prepare 2-(4-trifluoromethylphenyl)benzimidazole-4-carboxamide (**1**, NU1077) as a biological reference standard. The published synthesis [8] of **1** started with 3-nitrophthalic anhydride (**2**) (Scheme 1). The fifth step of the synthesis, the acylation of methyl 2,3-diaminobenzoate (**3**), was a particular problem, leading to only a 10% yield of methyl 2-(4-trifluoromethylphenyl)benzimidazole-4-carboxylate (**4**) following cyclization in acetic acid. A final step completed this seven-step synthesis in an overall yield of 1%. Not wishing to duplicate this synthesis, we sought an alternative preparation of **1**. We now wish to report that **1** may be conveniently prepared in a four-step sequence starting with commercially available 2,3-diaminotoluene (**5**) (Scheme 2).

Scheme 1



Scheme 2



Condensation of **5** and 4-trifluoromethylbenzaldehyde in the presence of sodium bisulfite afforded the corresponding benzimidazole **6** in 73% yield [9]. Numerous methods exist for the oxidation of heteroaromatic methyl groups to carboxylic acids. A majority of these oxidations rely on the use of either nitric acid at elevated temperatures, chromium trioxide in sulfuric acid, selenium dioxide, or potassium permanganate. In our case, we had to keep in mind that aromatic trifluoromethyl groups have been hydrolyzed to the corresponding carboxylic acids under both acidic [10] and alkaline conditions [11]. We also wished to avoid selenium dioxide for toxicity reasons. Ultimately, we found that the oxidation of **6** with potassium permanganate in aqueous *t*-butanol afforded the desired carboxylic acid **7** in 55% yield [12]. Carboxylic acid **7** was then converted to the corresponding acid chloride that, without purification, was treated with ammonium hydroxide to yield **1** in 53% yield.

In conclusion, we have developed a short synthesis of the PARP inhibitor 2-(4-trifluoromethylphenyl)benzimidazole-4-carboxamide (**1**, NU1077) that proceeded in an overall yield of 21%. The synthetic sequence should be amenable to the preparation of a variety of analogs providing that potential substituents are stable to the $KMnO_4$ oxidation conditions.

EXPERIMENTAL

All reagents and solvents were used as received. Ir spectra were determined using potassium bromide pellets. ^{1}H nmr spectra were recorded at 300 MHz. Mass spectra were recorded using EI methods. Flash chromatography was performed as previously described [13].

4-Methyl-2-(4-trifluoromethylphenyl)benzimidazole (**6**).

A solution of 4-trifluoromethylbenzaldehyde (14.25 g, 81.84 mmol) in methanol (50 mL) was added dropwise to a stirred mixture of 2,3-diaminotoluene (10.0 g, 81.8 mmol), sodium bisulfite (9.4 g, 90 mmol), and methanol (100 mL). The reaction was heated at reflux for 1 hour. After cooling to room temperature, the inorganic material was collected by filtration and rinsed with methanol (100 mL). The solvent was evaporated at reduced pressure and the resulting oil was dissolved in ethyl acetate (600 mL). The organic layer was washed successively with 0.2 *M* aqueous hydrochloric acid (2 x 200 mL), saturated aqueous sodium bicarbonate (2 x 200 mL) and saturated aqueous sodium chloride (2 x 200 mL). After drying over magnesium sulfate, the solvent was evaporated at reduced pressure. The resulting oil was purified by flash chromatography using the step gradient 10% ethyl acetate/hexane, 15% ethyl acetate/hexane affording 16.6 g (73%) of **6** as an off-white solid, mp 89-91 °C; ir (potassium bromide): 3117, 1445, 1332, 1321,1160, 1119, 1069, 846 cm^{-1}; ^{1}H nmr (dimethylsulfoxide-d_6): δ 12.95 (br s, 1H), 8.42 (d, 2H, *J* = 7.7 Hz), 7.93 (d, 2H, *J* = 8.0 Hz), 7.48-7.38 (m, 1H), 7.13 (t, 1H, *J* = 7.7 Hz), 7.03 (d, 1H, *J* = 7.3 Hz), 2.59 (s, 3H); ms (EI) *m/z* (rel intensity) 276 (M^+, 100%).

Anal. Calcd for $C_{15}H_{11}F_3N_2 \cdot 1/3H_2O$: C, 63.83; H, 4.17; N, 9.93. Found: C, 63,84; H, 4.00; N, 9.89.

2-(4-Trifluoromethylphenyl)benzimidazole-4-carboxylic Acid (**7**).

Benzimidazole **6** (1.8 g, 6.5 mmol) was stirred and warmed to approximately 50 °C in *t*-butanol (30 mL). A 50 °C solution of potassium permanganate (5.4 g, 34 mmol) in water (50 mL) was added in 5-10 mL portions over 2.5 hours so that the reaction temperature was maintained between 50-55 °C. The reaction was stirred overnight at approximately 55 °C. After cooling to room temperature, the precipitate was collected by filtration. The precipitate was washed with water (500 mL) that had been warmed to approximately 80 °C. The filtrate was extracted with ethyl acetate (3 x 150 mL) before being acidified with concentrated hydrochloric acid to pH = 2 (test paper). The aqueous layer was extracted with ethyl acetate (3 x 250 mL). The organic extracts were combined and dried over magnesium sulfate. The drying agent was removed by filtration and the filtrate was evaporated at reduced pressure to yield 1.1 g (55%) of **7** as a colorless solid, mp >300 °C; ir (potassium bromide): 3296, 1671, 1321, 1286, 1260, 1236, 1209, 1189, 1181, 1149, 1142, 1112, 1068 cm^{-1}; ^{1}H nmr (dimethylsulfoxide-d_6): δ 12.7 (br s, 1H), 8.55 (d, 2H, *J* = 7.5 Hz), 8.02-7.84 (m, 4H), 7.40-7.32 (m, 1H); ms (EI) *m/z* (rel intensity) 306 (M^+, 100%).

Anal. Calcd for $C_{15}H_9F_3N_2O_2$: C, 58.83; H, 2.96; N, 9.15. Found: C, 58.72; H, 3.07; N, 9.10.

2-(4-Trifluoromethylphenyl)benzimidazole-4-carboxamide (**1**, NU1077).

Oxalyl chloride (1.0 mL, 11 mmol) was added dropwise to a stirred suspension of carboxylic acid **7** (1.7 g, 5.6 mmol), dry dimethylformamide (4 drops) and dry tetrahydrofuran (60 mL). After stirring at room temperature for 2 hours, the solvent was evaporated at reduced pressure. The resulting solid was suspended in dry tetrahydrofuran (100 mL) and ammonium hydroxide (2.0 mL, 30 mmol) was added dropwise. After 2 hours, the solvent was evaporated at reduced pressure. The concentrate was partitioned between ethyl acetate (800 mL) and water (100 mL). The layers were separated and the organic layer was washed with saturated aqueous sodium bicarbonate. After drying over magnesium sulfate, the ethyl acetate was evaporated at reduced pressure. The resulting solid was triturated with hot methanol (10 mL). The product was collected by filtration, washed with methanol, and dried by suction affording 0.90 g (53%) of **1** as a colorless solid, mp >300 °C; ir (potassium bromide): 3161, 1164, 1597, 1327, 1315, 1170, 1115, 1066 cm^{-1}; ^{1}H nmr (dimethylsulfoxide-d_6): δ 13.70 (s, 1H), 9.30 (s,1H), 8.50-7.77 (m, 7H), 7.45-7.38 (m, 1H); ms (EI) *m/z* (rel intensity) 305 (M^+, 100%).

Anal. Calcd for $C_{15}H_{10}F_3N_3O$: C, 59.02; H, 3.30; N, 13.77. Found: C, 58.83; H, 3.28; N, 13.57.

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