Triazolopyridines 23.[1] Synthesis of 5,5'-bi[1,2,3]triazolo[5,1-*a*]isoquinoline

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Dedicated to Professor Enrique Meléndez on his 70th birthday

(received 08 Oct 03; accepted 05 Dec 03; published on the web 09 Dec 03)

Abstract

5,5'-Bi[1,2,3]triazolo[5,1-*a*]isoquinoline **6** has been synthesised from [1,2,3]triazolo[5,1-*a*] isoquinoline **5** by four procedures, dimerisation by LDA, Stille and Suzuki self-coupling reactions, and Suzuki cross-coupling reaction. The last is the best. Compound **6** gives 1,1'-bi(acetoxymethyl)-3,3'-biisoquinoline **10** by triazolo ring opening by acetic acid.

Keywords: Bitriazoloisoquinolines, triazoloisoquinolines, lithiation reaction, self-coupling and cross-coupling reactions

Introduction

The preparation and utilization of biheteroaryl systems is a demanding goal,[2] seeing that they are interesting compounds with numerous potential fields of applications as electrical or electronic materials,[3] as monomers for the synthesis of conductive polymers,[4] with rich photophysical and photochemical properties,[5] and as luminescent molecular sensors.[6] Incorporation of biheteroaryls into macropolycyclic structures leads to very interesting ligands to form photoactive cryptates of interest as novel luminescent material.[7] The formation of helicates, helices incorporating metal ions, as versatile supramolecular complexes[8] is another important potentiality of biheterocycles. In the context of our work on triazolopyridines **1**, we have reported the synthesis of the new biheteroaryl system 7,7'-bitriazolopyridine **2** by dimerisation of [1,2,3]triazolo[1,5-*a*]pyridines with LDA, the use of compounds **2** to produce 2,2'-bipyridines **3**,[9] and the synthesis of potential helicating ligands like **4**.[10] We wish to report here our results on the application to

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[1,2,3]triazolo[5,1-*a*]isoquinoline **5** of the cited methodology,[11] with the aim to synthesise novel biheterocycles to study their chemical reactions and applications. (Figure 1).

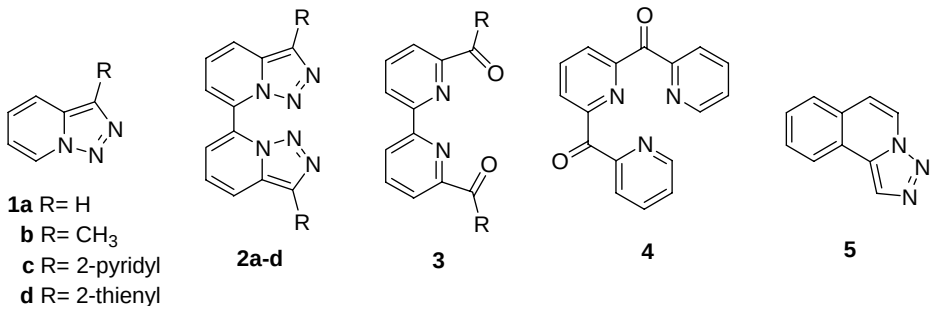


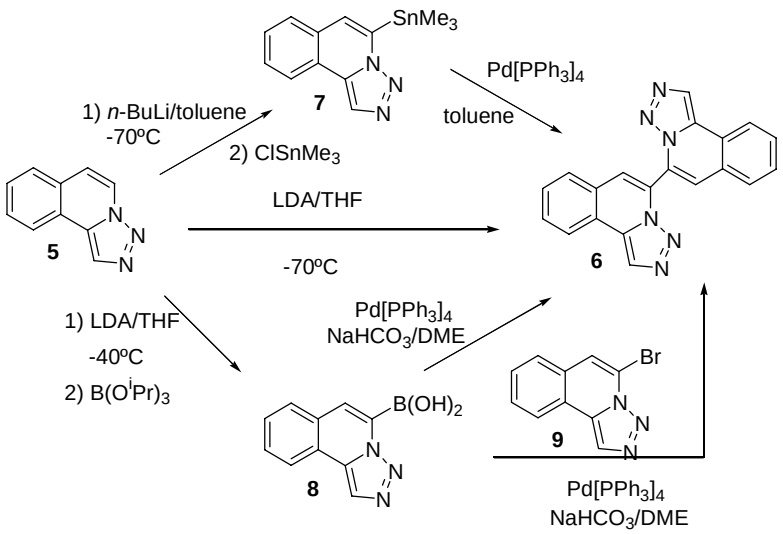
Figure 1

Results and Discussion

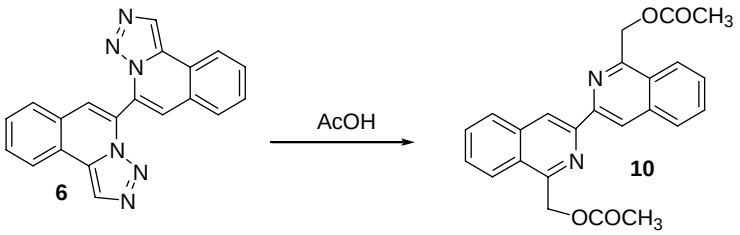
As we have reported, the reaction between triazoloisoquinoline **5** and lithium di-isopropylamide (LDA) in ether, or *n*-BuLi in toluene, at –40ºC gives a 5-lithio derivative, trapped by electrophiles.[12,13] We have now discovered that the reaction was strongly temperature/solvent/ lithium reagent dependent. At –70ºC, in THF as solvent and LDA as lithium reagent, a new reaction occurs, and the interesting biheterocycle 5,5'-bi[1,2,3]triazolo[5,1-*a*]isoquinoline **6** was formed in moderate yield (55%), from 60% of starting material that was recovered after work-up. Several attempts were made to improve the yield and were unsuccessful. The reaction was difficult to reproduce, and polymeric material was formed in some attempts. The interest of the compound let us to achieve new routes to synthesise it.

Biheterocycles are now readily available by way of palladium-catalyzed self-coupling reactions, such as the Stille[14] and the Suzuki procedures.[15] There are not precedents in literature about these reactions in triazolopyridine chemistry, neither stannanes or boronic acid derivatives are known. We have prepared 5-trimethylstannyl-[1,2,3]triazolo[5,1-*a*]isoquinoline **7** and [1,2,3]triazolo[5,1-*a*]isoquinolyl-5-boronic acid **8**, both are stable solids (see experimental). Homocoupling reactions were done with tetrakis(triphenylphosphine)palladium(0) as catalyst, reactions were clean and also moderate yields of compound **6** were obtained. A new attempt to improve the yield was made, the Suzuki cross-coupling reaction was done with triazoloisoquinoline boronic acid **8** and the corresponding triazoloisoquinoline halide **9**, with this last procedure a very good yield of the required dimer was obtained (89%). (Scheme 1).

5,5'-Bi[1,2,3]triazolo[5,1-*a*]isoquinoline **6** could be a precursor of 1,1'-disubstituted-3,3'-biisoquinolines, other interesting biheterocycles,[2] if the known reaction in triazoloisoquinolines,[12] triazolo ring open with loss of nitrogen, is general. The reaction of compound **6** with acetic acid proceeded as expected giving compound **10** in good yield. (Scheme 2).



Scheme 1



Scheme 2

Experimental Section

General Procedures. Melting points were determined on a Kofler heated stage and are uncorrected. NMR spectra were recorded on a Bruker AC300MHz in $CDCl_3$ as solvent. HRMS (EI) determinations were made using a VG Autospec Trio 1000 (Fisons). ESI-MS was performed using an ion trap mass spectrometer (Esquire 3000 Plus, Bruker) coupled to a liquid chromatograph (Agilet LC 1100 Chemstation), the ionization method was electrospray with positive ion polarity (ESI+). Samples were dissolved in acetonitrile/water (2/3) containing 0.5% formic acid. Chromatography was performed on a Chromatotron, using 2 cm plates of silica Merck Pf254.

[1,2,3]Triazolo[5,1-*a*]isoquinoline (5). Prepared as described.[12]

Lithiation reaction of [1,2,3]triazolo[5,1-*a*]isoquinoline (5) at –70ºC. A solution of *n*-BuLi in hexane (3.7mL, 1.6M) was added to diisopropylamine, freshly distilled from KOH (0.8mL) at –70ºC, under argon. A solution of [1,2,3]triazolo[5,1-*a*]isoquinoline **5** (1g, 5.91mmol) in anhydrous THF (40mL) was added with stirring. A deep red colour developed. The mixture was kept at –70ºC (10h) and then at room temperature (48h) during which time the solution became

yellow. Then was hydrolysed with saturated solution of ammonium chloride (50mL). Extraction with dichloromethane gave after drying and evaporation of organic solvent a residue which was purified by chromatography. Elution with ethyl acetate/hexane (2:1) gave starting material (0.6g). Further elution gave the white solid **5,5'-bi[1,2,3]triazolo[5,1-*a*]isoquinoline (6)** (0.22g, 22%), m.p. 288ºC (DMSO). HRMS (EI) found for M^+ 336.1123; $C_{20}H_{12}N_6$ requires 336.1123. ^{1}H NMR δ (DMSO) 8.02 (s,2H); 7.65 (d, J=7.7Hz, 2H); 7.24 (d, J=8.0Hz, 2H); 7.21 (s, 2H); 7.06-6.89 (m, 4H). ^{13}C NMR δ (DMSO) 132.45 (C); 130.32 (C); 129.84 (CH); 128.60 (CH+C); 126.82 (CH); 126.55 (C); 124.55 (CH); 122.93 (C); 119.64 (CH).

5-Trimethylstannyl-[1,2,3]triazolo[5,1-*a*]isoquinoline (7). To a solution of [1,2,3]triazolo[5,1-*a*]isoquinoline (614mg, 3.55mmol) in toluene (40mL) was added *n*-butyllithium (1.5mL, 2.5M in hexane) with stirring at –70ºC. A deep red colour developed. The solution was stirred for 2h at –70ºC and trimethyltin chloride (3.22mL, 1.1M in THF) was added. The mixture was kept a –70ºC (4h) and then at room temperature (48h), during which time the solution became yellow. Distilled water (25mL) was added along with diethyl ether (3x25mL) and decanted. The organic phase was washed with saturated NaH_3PO_4 (2x25mL), water, and brine, then dried (Na_2SO_4) and evaporated. The crude product was purified by chromatotron, eluting with hexane/ethyl acetate 9:1 gives **5-trimethylstannyl-[1,2,3]triazolo[5,1-*a*]isoquinoline (7)** as an oil (0.52g, 43%). Crystallised from hexane, m.p. 93ºC. HRMS (FAB) found for $(M+H)^+$ 334.0376; ($C_{13}H_{15}N_3{}^{120}$Sn + H) requires 334.0366. ^{1}H NMR δ (Cl_3CD) 8.32 (s, 1H); 8.10-8.00 (m, 1H); 7.70-7.60 (m, 1H); 7.61-7.55 (m, 2H); 7.16 (s, 1H); 0.47 (t, J_{HSn}=29Hz, 9H). ^{13}C NMR δ. (Cl_3CD) 139.86 (C); 131.23 (C); 129.00 (C); 128.67 (CH); 128.22 (CH); 126.87 (CH); 125.59 (CH); 124.32 (CH); 124.12 (CH); 123.18 (CH); -8.55 (CH_3). Further elution gives starting material (275mg).

Homocoupling reaction of 5-trimethylstannyl-[1,2,3]triazolo[5,1-*a*]isoquinoline (7). A mixture of 5-trimethylstannyl-[1,2,3]triazolo[5,1-*a*]isoquinoline **7** (0,25g, 0,75mmol), tetrakis(triphenylphosphine)palladium(0) (0,043g) and dry toluene (10mL) was stirred at reflux for 4 days, then was cooled and a solid was formed. The mixture was filtered, washed with ethyl ether, and a white solid (0.085g) was identified as **5,5'-bi-[1,2,3]triazolo[5,1-*a*]isoquinoline 6**. The filtrate was evaporated and was purified by chromatotron using ethyl acetate/hexane as eluent. Two fractions were separated, 5,5'-bi-[1,2,3]triazolo[5,1-*a*]isoquinoline **6** (0.02g) and traces of triazoloisoquinoline. Total yield of **6** was 53%.

[1,2,3]Triazolo[5,1-*a*]isoquinolyl-5-boronic acid (8). To a solution of [1,2,3]triazolo[5,1-*a*]isoquinoline (1.17g, 6.93mmol) in dry toluene (30mL) cooled to –40ºC was added *n*-butyllithium (2.8mL, 2.5M in hexane) with stirring at –40ºC. A deep red colour developed. The solution was stirred and kept at this temperature 3 h. A solution of triisopropyl borate (1.2 equiv.) in toluene was then added and the mixture was allowed to react at this temperature for over 2 h, and then allowed to warm to room temperature. The mixture was quenched by slow addition of 4% aqueous NaOH solution (50 mL), a white solid was formed and filtered. The resulting aqueous layer was collected and acidified down to pH=5 by dropwise addition of concentrated HCl, keeping the internal temperature below 5ºC. A white solid was formed, filtered and washed with ether. Both solids were identified as **[1,2,3]Triazolo[5,1-*a*]isoquinolyl-**

5-boronic acid (8). (1.08g, 78%). m.p. >310ºC. Characterized by ESI-MS found for M^+ 212/213; $C_{10}H_8BN_3O_2$ requires 212/213. ^{1}H NMR δ (D_2O/NaOH) 8.36 (s,1H); 7.96 (d, J=7.6Hz, 1H); 7.66 (d, J=7.3Hz, 1H); 7.48-7.36 (m, 2H); 7.20 (s, 1H).

Homocoupling reaction of the [1,2,3]triazolo[5,1-*a*]isoquinolyl-5-boronic acid (8). A mixture of [1,2,3]triazolo[5,1-*a*]isoquinolyl-5-boronic acid **8** (0.085g, 0.04mmol), $Pd[PPh_3]_4$ (0.023g, 0.039mmol), DME (10mL), sodium hydrogen carbonate (0.1g, 1,2mmol) and water (5mL) was refluxed under nitrogen with vigorous stirring (24h). Water was added (50mL) and the mixture was extracted with dichloromethane (3x50mL). The organic layer was dried (Na_2SO_4) and removed under reduced pressure. The reaction crude was purified by chromatotron using ethyl acetate/hexane as eluent. Triazoloisoquinoline was obtained in the first fraction (0,0175g, 26%) and 5,5'-bi-[1,2,3]triazolo[5,1-*a*]isoquinoline **6** (0.03g, 46%) in the second .

5-Bromo-[1,2,3]triazolo[5,1-*a*]isoquinoline (9). Prepared as described.[13]

Cross-coupling reaction between [1,2,3]triazolo[5,1-*a*]isoquinolyl-5-boronic acid (8) and 5-bromo-[1,2,3]triazolo[5,1-*a*]isoquinoline (9). A mixture of [1,2,3]triazolo[5,1-*a*]isoquinolyl-5-boronic acid **8** (0.085g, 0.04mmol), DME (10mL), sodium hydrogen carbonate (0.1g, 1.2mmol) and water (5mL) was heat at 45ºC under nitrogen with vigorous stirring (24h). Then a solution of 5-bromo-[1,2,3]triazolo[5,1-*a*] isoquinoline **9** (0.078g, 0.31mmol), $Pd[PPh_3]_4$ (0.023g, 0.039 mmol) in DME (5mL) was added. The reaction was refluxed with vigorous stirring under nitrogen atmosphere and the reaction was followed by tlc. (24h). Water was added (50mL) and the mixture was extracted with dichloromethane (3x50mL). The organic layer was dried (Na_2SO_4) and removed under reduced pressure. The reaction crude was purified by chromatotron using ethyl acetate/hexane as eluent. Triazoloisoquinoline was obtained in the first fraction (0.01g) and 5,5'-bi-[1,2,3]triazolo[5,1-*a*]isoquinoline **6** (0.0985g, 89%) in the second.

1,1'-Bi(acetoxymethyl)-3,3'-biisoquinoline (10). A solution of 5,5'-bi[1,2,3]triazolo[5,1-*a*]isoquinoline **6** (89mg, 0,26mmol) in glacial acetic acid (1mL) was boiled (2h). Cooled, neutralized (aq. $NaHCO_3$), and extracted with dichloromethane. The organic layers were dried, filtered, and evaporated. The reaction crude was purified by chromatotron. Elution with ethyl acetate/hexane 3:7 gave **1,1'-bi(acetoxymethyl)-3,3'-biisoquinoline 10** (78mg, 74%) as an oil. HMRS (EI) found for M^+ 400.1428; $C_{24}H_{20}N_2O_4$ requires 400.1423. NMR ^{1}H δ (Cl_3CD) 8.87 (s, 2H); 8.07 (d, J=8.5Hz, 2H); 7.95 (d, J=8.1Hz, 2H); 7.68 (ddd, J=8.1Hz, J=6.8Hz, J=1.1Hz, 2H); 7.57 (ddd, J=8.5Hz, J=6.8Hz, J=1.3Hz, 2H); 5.77 (s, 4H); 2.16 (s, 6H). NMR ^{13}C δ. (Cl_3CD) 170.59 (CO); 153.87 (C); 148.39 (C); 137.17 (C); 130.19 (CH); 128.38 (CH); 127.57 (CH); 126.51 (CH); 124.56 (CH); 118.15 (CH); 65.96 (CH_2); 20.85 (CH_3).

Acknowledgements

Our thanks are due to Secretaría de Estado de Política Científica y Tecnológica del Ministerio de Ciencia y Tecnología, Spain (project BQU 2003-09215-C03-03) for it finalcial support and to the

Vicerrectorado de Política Científica y Relaciones Exteriores de la Universidad de Valencia for a grant to J. R. D.

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