Addendum

Supporting information

MOLECULAR PHARMACEUTICS VOL. 5, No.3, 430-437

Induced disorder in protein-ligand complexes as a drug design strategy

By: Alejandro Crespo and Ariel Fernández

Alternative synthesis of intermediate compound 4 (I → II → III → 4)

The total synthesis of compound **4**, an intermediate in the preparation of the entropy-jolting molecular prototype (scheme in **Supporting Information**), can be alternatively carried out easily using commercially available reactants¹. 3-acetyl-pyridine (**3**) was originally identified as the starting material for the preparation of compound **4** in **Supporting Information** (see figure below). We now report on an alternative route that makes use of commercially available 1-(3-pyridyl)-3-(dimethylamino)-2-propen-1-one (**I**) (CAS registry number 55314-16-4; Ryan Scientific, Mt Pleasant, SC) as the starting compound. The synthesis starts with bromination of **I**, followed by removal of HBr to yield 1-(3-pyridyl)-3-(dimethylamino)-2-propin-1-one (**III**). Compound **III** is subsequently treated with HCl to yield 1-(3-pyridyl)-3-chloro-3-(dimethylamino)-2-propen-1-one (**4**). This alternative synthetic route is schematized in the figure below:

1-(3-pyridyl)-3-(dimethylamino)-2-bromo-2-propen-1-one (II): A solution of 10g of commercially available 1-(3-pyridyl)-3-(dimethylamino)-2-propen-1-one (I) in 40ml of absolute CH_2Cl_2 under nitrogen atmosphere at 0°C is treated for 1hr with 16g bromine. The solution is then treated with 12g triethylamine dissolved in 50ml ether and stirred for 1 hr at 0°C . Triethylamonium bromide precipitates and is removed by filtration and the supernatant evaporated and distilled to produce 12.1g (yield 83%) of compound II. δ ^1H -NMR (DMSO): 9.09 (s, 1H), 8.66 (d, $J= 4.7$ Hz, 1H), 8.40 (s, 1H), 8.09 (d, $J= 8.2\text{Hz}$, 1H), 7.62 (dd, $J=8.2, 5.0$ Hz, 1H), 3.02 (s, 6H).

1-(3-pyridyl)-3-(dimethylamino)-2-propin-1-one (III): To a solution of 14 g of II in 50 ml THF we add within 3 hours at 0°C a solution of 3 g potassium in 100 ml THF and 33 ml absolute t-butanol. The mixture is stirred for 2 hours under nitrogen atmosphere (an excess of potassium-ter-butoxi must be avoided!). We then remove the precipitated KBr/ter-butanol by centrifugation and evaporate the solution at 12 torr/ 10° and obtain ~8 g of a brown-red oily substance. Evaporation at 10^{-4} torr in a container pre-cooled at -25°C yields 5.0 g (yield 52%) of colorless crystals. Compound III is stable for several days at -25°C but polymerizes within the hour at room temperature. δ ^1H -NMR (CDCl_3): 8.92 (s, 1H), 8.51 (d, $J= 4.7$ Hz, 1H), 8.07 (d, $J= 8.1$ Hz, 1H), 7.52 (dd, $J= 8.0, 4.9$ Hz, 1H), 3.32 (s, 6H).

Compound 4: To a solution of 1.0 g 1-(3-pyridyl)-3-(dimethylamino)-2-propin-1-one (III) in 10 ml THF we add 10 ml of HCl 1M in THF at -20°C . After 1 hour at -20°C , the initial precipitate dissolves. Evaporation at 12 torr/ 0° produces 1.1 g (yield 91%) of compound 4. MW: 210.51. δ ^1H -NMR (DMSO): 8.82 (s, 1H), 8.57 (d, $J= 4.8$ Hz, 1H), 8.09 (d, $J= 8.1$ Hz, 1H), 7.58 (dd, $J= 8.2, 5.0$ Hz, 1H), 5.74 (s, 1H), 3.20 (s, 6H).

Reference:

1. Gais, H. J.; Hafner, K.; Neuenschwander, M. Acetylene mit Elektronendonator und Elektronenakzeptorgruppen. *Helvetica Chim. Acta* **1969**, 52, 2641-2657.