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NOTE

Regioselective Mono-bromination of Pyrrolo[2,1-f][1,2,4]triazin-4-amine

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Pyrrolo[2,1-f][1,2,4]triazin-4-amine is regioselectively brominated when treated with 1,3-dibromo-5,5-dimethylimidazolidine-2,4-dione in different solvents. The brominated product, 5,7-dibromopyrrolo[2,1-f][1,2,4]triazin-4-amine predominates when the reaction is run in dichloromethane. The subsequent debromination process utilizes lithium-bromine exchange to give the desired product 5-bromo-pyrrolo[2,1-f][1,2,4]triazin-4-amine.

Keywords: Over-bromination, Lithium-bromine exchange.

Among the most routinely conducted organic transformations, bromination is undoubtedly irreplaceable in synthetic chemistry. For alkyl bromides, the brominated position provides a good site for subsequent nucleophilic substitution. On the other hand, as versatile intermediates, aromatic bromides are ideal precursors in transition metal-catalyzed coupling reactions, namely Suzuki reaction and the like. Mechanistically, a bromination process can proceed *via* quite different pathways. For the instance of alkyl benzenes, bromination occurs either at the benzylic position by free radical or on the benzene ring through aromatic substitution (S_NAr), according to the brominating agent and the specific reaction condition.

Pyrrolo[2,1-f][1,2,4]triazin-4-amine has a [6,5] fused heterocyclic ring. Containing multiple nitrogen atoms, it has caught attention from the pharmaceutical industry[1-5]. Chemical structures further derived from it have demonstrated excellent biological activities in therapeutic fields such as cancer[1,4,5], angiogenesis[1,2], ocular disorder[2], and neuro degenerative disorder[3]. These molecules are prepared by regioselective bromination of the title compound, followed by one of the coupling reactions, typically Suzuki reaction.

In literature, the positions 5 and 7 of pyrrolo[2,1-f][1,2,4]-triazin-4-amine could be selectively brominated just by using different solvents (N,N'-dimethyl formamide *vs.* dichloromethane) with the same brominating agent 1,3-dibromo-5,5-dimethylimidazolidine-2,4-dione (Fig.1). However, this bromination step turned out to be troublesome in practice. Bromination at position 5 would not stop at the single substitution stage. Instead, it continued to take place at position 7, resulting in 5,7-dibromopyrrolo[2,1-f][1,2,4]-triazin-4-amine. In order to generate new leads, monosubstituted bromide at different positions of the 5-membered ring of the title compound was desired and over-bromination needed to be avoided.

For the 5-membered ring, positions 5, 6 and 7 are all likely to be brominated. However, by examining the structure of pyrrolo[2,1-f][1,2,4]triazin-4-amine, we find the electron density at position 7 is higher than that at position 5. That is to say, in electronic bromination reactions, position 7 is more reactive than position 5. This explains why it is not possible to get 5-bromopyrrolo[2,1-f][1,2,4]triazin-4-amine without a significant amount of disubstituted bromide. It is the intrinsic trend that determines when dichloromethane is the solvent, only 1/3 of the product is exclusively brominated at position 5 while the rest 2/3 is at both position 5 and position 7.

To overcome this hurdle, an alternative route was taken. After numerous fruitless attempts to increase the amount of the 5-brominated product, we decided to convert the 5,7-dibromide, previously considered as a by-product, to the desired 5-bromide. We rationalized that the bromine molecule at position 7 was supposedly more prone to lithium-halogen exchange, since this position is more reactive in electronic substitution reactions than position 5. To test our assumption, we monitored the progress of the exchange by TLC while treating the isolated 5,7-dibromopyrrolo[2,1-f][1,2,4]triazin-4-amine with *n*-butyl lithium. Gratifyingly, not only debromination took place rapidly but the transformation was also rather

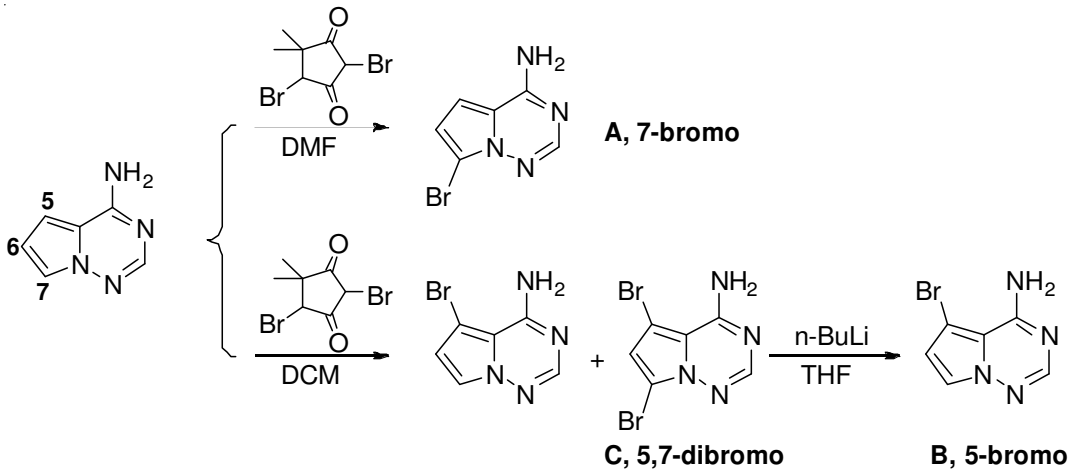

Fig. 1. Regioselective bromination of pyrrolo[2,1-f][1,2,4]triazin-4-amine

clean. After aqueous workup, the resulting solution from this *n*-butyl lithium titration contained almost exclusively the desired 5-bromopyrrolo[2,1-f][1,2,4]triazin-4-amine. (Fig. 1)

Synthesis of 7-bromopyrrolo[2,1-f][1,2,4]triazin-4-amine: A stirred solution containing pyrrolo[2,1-f][1,2,4]-triazin-4-amine (10 g, 75 mmol) in anhydrous N,N-dimethylformamide (100 mL) was cooled to -20 °C and 1,3-dibromo-5,5-dimethylhydantoin (10.7 g, 37.4 mmol) was added portionwise over 45 min. The reaction was stirred for another 45 min and monitored by TLC. After completion, the reaction mixture was washed with saturated aqueous solution of sodium sulfite (150 mL) and water. It was then partitioned between ethyl acetate (0.5 L) and 5 % aqueous solution of sodium carbonate (500 mL). The organic layer was washed with aqueous solution of sodium carbonate, dried and concentrated to afford 13.3 g crude product. It was purified by silica gel column chromatography (CH_2Cl_2:MeOH = 100:1) to give the 7-bromo compound as a white crystal (12.3 g, 77 %).

Synthesis of 5-bromopyrrolo[2,1-f][1,2,4]triazin-4-amine: A suspension of pyrrolo[2,1-f][1,2,4]triazin-4-amine (10 g, 75 mmol) in dichloromethane (100 mL) was stirred and cooled to -10 °C under nitrogen. A solution of 1,3-dibromo-5,5-dimethylimidazolidine-2,4-dione (10.8 g, 37.8 mmol) in dichloromethane (2 L) was added dropwise over 1 h. After 4 h, 2 L of 10 % aqueous solution of Na_2SO_3 was added and the mixture was stirred vigorously for a few minutes. The organic phase was washed with water, then brine, dried, filtered and concentrated *in vacuo* to give a mixture of the 5,7-dibromo compound and the 5-bromo compound (13 g, 2:1). A suspension of this mixture (10 g in 200 mL THF) was titrated with *n*-butyl lithium dropwise at -60 °C and the progress was monitored by TLC and LC/MS to determine the end point. The reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic phase was washed with brine, dried and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 3:1) to give the 5-bromo compound as a white solid (4 g).

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