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THE SYNTHETIC UTILITY OF p-NITROPHENYL 3-BROMO-2,2-DIETHOXYPROPIONATE

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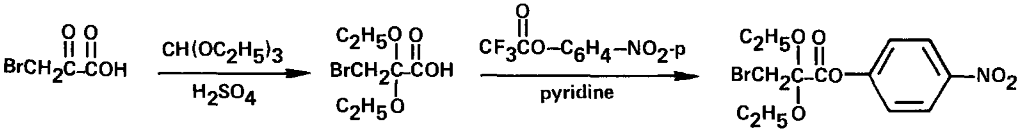
Summary: The synthesis of p-nitrophenyl 3-bromo-2,2-diethoxypropionate, and its chemoselective reactions for the preparation of highly functionalized small molecules and also novel heterocycles, are described.

Highly functionalized small molecules that can be chemoselectively manipulated are of great value to the synthetic organic chemist. Of particular interest would be a derivative of a 3-halopyruvic acid in which the acid moiety is activated toward nucleophilic attack. Such a molecule would consist of an α-haloketone linked directly to an activated carboxylic acid, and would contain, in effect, three contiguous electropositive carbon atoms. Clearly, chemoselectivity in the reactions of such a molecule with nucleophiles would be difficult to realize, unless the molecule is designed in such a way that each carbon atom could be differentiated. Furthermore, for a synthon of this type to be of general utility, it should be readily available on large scale, and be reasonably stable. A reagent which meets these criteria is p-nitrophenyl 3-bromo-2,2-diethoxypropionate (NPBDP, 1), and this work describes the utility of 1 in the synthesis of highly functionalized small molecules, as well as heterocycles.

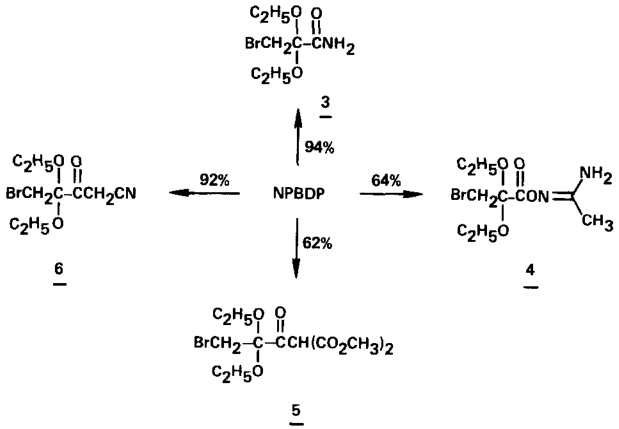
NPBDP[2] possesses an α-bromoketone moiety masked as a ketal, along with an active carboxylic ester. It is readily prepared in 100 g quantities in 77% overall yield by ketalization of commercially available α-bromopyruvic acid, followed by reaction of this ketal (2) with p-nitrophenyl trifluoroacetate.[1] NPBDP is a crystalline solid, mp 75-76°C, which can be stored routinely for over a year without decomposition.



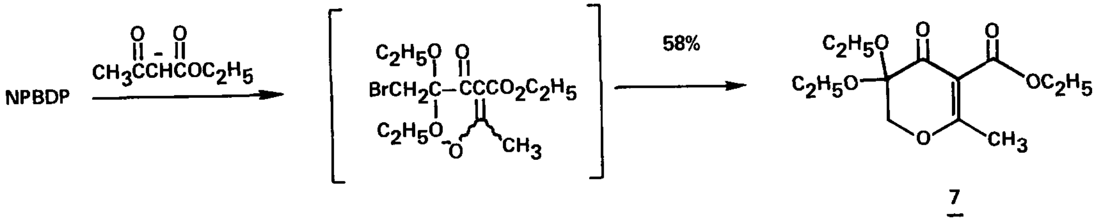
NPBDP

2 1

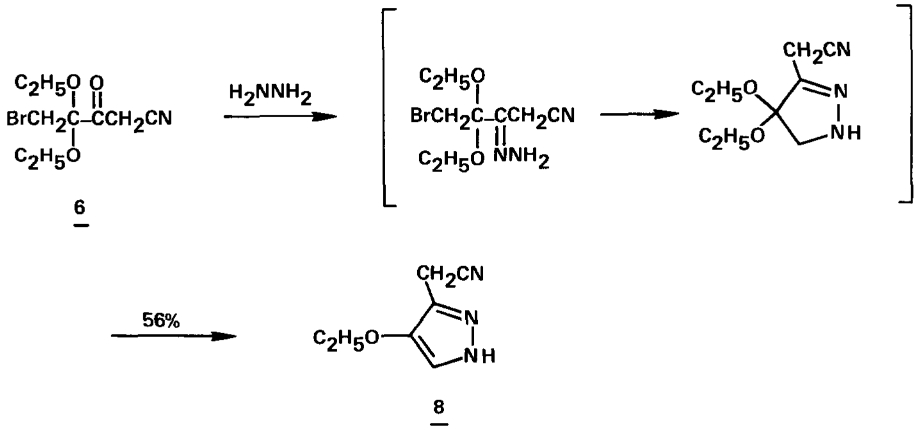
The neopentyl-like structure of NPBDP hinders nucleophilic attack at the α-bromo carbon atom, and, thus, a wide variety of nucleophiles react exclusively at the active ester. For example, ammonia and acetamide oxime react smoothly with NPBDP to give amide 3 (94%) and adduct 4 (64%) respectively. The sodium salt of dimethyl malonate affords 62% of diester 5. Even a potent nucleophile such as α-lithioacetonitrile reacts chemoselectively with NPBDP to afford 92% of the β-ketonitrile 6.



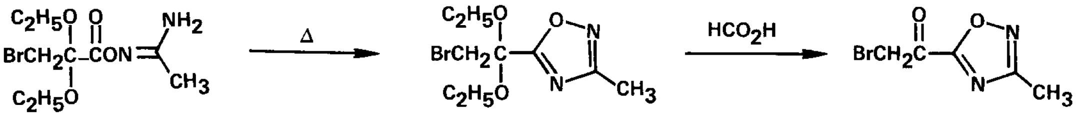
Although the α-bromoketal is inert to intermolecular reaction, intramolecular reactions can occur when bifunctional nucleophiles are employed. For example, treatment of NPBDP with the sodium salt of ethyl acetoacetate affords 58% of the highly functionalized 2,3-dihydro-γ-pyrone 7, a member of a family of compounds used in natural product synthesis.[3]



Another interesting cyclization occurs when 5-bromo-4,4-diethoxy-3- oxovaleronitrile (6) is treated with hydrazine. In this case, hydrazone formation is followed by intramolecular cyclization. Elimination of ethanol results in a 56% yield of pyrazole 8, the only product isolated in this reaction. This pyrazole substituent pattern would be difficult to obtain using classical syntheses.

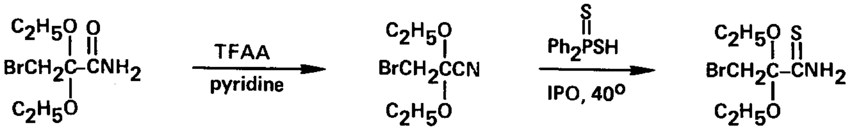


When desired, the α-bromoketal can be converted to the corresponding α-bromoketone using specific conditions. This is best demonstrated by the following sequence of reactions. Adduct 4 on treatment with p-toluenesulfonic acid (p-TsOH) in refluxing toluene readily cyclizes to the 1,2,4- oxadiazole, 9. Compound 9 is inert to mild deketalization (p-TsOH, acetone, reflux; 1N hydrobromic acid, room temperature). This resistance to deketalization is probably due to the difficulty in generating a carbonium ion which is flanked by two electropositive centers. Furthermore, the acid sensitive 1,2,4-oxadiazole moiety of 9 decomposes upon heating in mineral acids. Deketalization of 9 is achieved, however, using 95% formic acid at 85°C thereby affording α-bromoketone 10.



4 9 10

The compounds described above can also be further manipulated. For example, propionamide 3 is easily converted to propionitrile 11 (72%) using trifluoroacetic anhydride/pyridine.[4] Nitrile 11 can then be converted to thioamide 12 (53%) using Benner's procedure (Ph_2PS_2H, 2-propanol, 40°C).[5] Since both nitriles and thioamides are useful building blocks for the preparation of a variety of five-membered heterocyclic rings, 11 and 12 should be of value in heterocyclic synthesis.



3 11 12

NPBDP is thus a valuable reagent for the synthesis of a variety of highly functionalized small molecules, as well as for the preparation of a number of heterocycles. The further utility of NPBDP in heterocyclic synthesis will be reported in a full account of this work.

Synthesis of NPBDP: A solution of 100 g (0.60 mol) of bromopyruvic acid, 240 mL of triethylorthoformate, and 4 mL of concentrated sulfuric acid was stirred at room temperature for 24 h. The mixture was diluted with 1.2 L of methylene chloride, and the organic solution was washed successively with water (2 x 100 mL) and saturated sodium chloride solution (1 x 100 mL). The organic solution was dried, filtered, and evaporated, leaving a white solid which was dried *in vacuo* for 4 h, thereby affording 144 g (99%) of 3-bromo-2,2-diethoxypropionic acid (**2**) as a white solid, mp 80-85°C. This material was generally used directly in the next step. However, pure **2** (mp 91-92°C) can be prepared by recrystallization from cyclohexane.

A mixture of 144 g (0.60 mol) of **2**, 141 g (0.60 mol) of *p*-nitrophenyl trifluoroacetate,[2] and 450 mL of pyridine was stirred at room temperature under nitrogen for 24 h. The mixture was poured into 2.0 L of water, and this aqueous mixture was extracted with ether (4 x 500 mL). The combined extracts were washed with 5% NaOH solution (5 x 175 mL), then dried (Na_2SO_4), filtered, and evaporated, leaving an oil which solidified after brief scratching with a glass rod. Recrystallization from hexane afforded 169 g (77%) of NPBDP as a white crystalline solid, mp 75-76°C.[6]

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