SYNLETT Spotlight 459

This feature focuses on a reagent chosen by a postgraduate, highlighting the uses and preparation of the reagent in current research

2-Halobenzamides

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Introduction

2-Halobenzamides are important precursors in organic synthesis to construct various heterocyclic compounds. They exhibit strong intermolecular N–H···O=C hydrogen bonding^{1a} and therefore, most of them are crystalline solids in nature and can be stored for a long period of time. Most of the 2-halobenzamides are soluble in organic solvents, for example, in dichloromethane, chloroform, acetone, methanol, etc.

Preparation

2-Halobenzamide can be easily prepared from the corresponding 2-halobenzoyl chloride and freshly distilled primary amine in the presence of triethylamine.^{1a–e} Dichloromethane, chloroform, tetrahydrofuran, etc. are suitable solvents for this reaction.

Scheme 1 Synthesis of 2-halobenzamides

Abstracts

(A) Synthesis of Isoquinolones:

Cheng and colleagues described an efficient nickel-catalyzed method for the synthesis of substituted 1(2*H*)-isoquinolones via annulation of variously substituted 2-halobenzamides with alkynes. The reaction worked well with both internal and terminal alkynes. Here, Ni(II) is reduced to Ni(0) by zinc powder, followed by oxidative addition of 2-halobenzamide to Ni(0) to form a five-membered nickelacycle. The insertion of alkyne gave a seven-membered nickelacycle which upon reductive elimination yielded the isoquinolone.²

(B) Synthesis of Isocoumarins:

Isocoumarins are well-known heterocyclic scaffolds for the construction of various natural products possessing a wide range of biological activities. Yao and co-workers described an efficient synthesis of isocoumarins by a copper-catalyzed tandem C–C/C–O coupling strategy by utilizing various 2-iodo-*N*-phenylbenzamides and acyclic 1,3-diketones as starting materials.³ By using a cyclic ketone as starting material the isoquinolinone is produced.

(C) *Synthesis of Chalcogen-N Heterocycles:*

Kumar and colleagues described a copper-catalyzed methodology for the construction of heterocyclic compounds bearing a Se–N or S–N bond.⁴ 2-Halobenzamides are treated with elemental selenium or sulfur in the presence of CuI catalyst and K₂CO₃ as base.

(D) *Synthesis of 2-Hydroxybenzamides:*

The 2-hydroxybenzamide motif has a wide range of biological activities. Kumar and co-worker described an efficient methodology for the synthesis of 2-hydroxybenzamides from the corresponding 2-chlorobenzamides by using CuI/1,10-phenanthroline.⁵ This is the first report of a copper-catalyzed hydroxylation in neat water.

(E) *Synthesis of Phenanthridinones:*

Synthesis of phenanthridinones is described from 2-halobenzamides in the presence of KO^tBu by using a catalytic amount of 1,10-phenanthroline or AIBN. The reaction proceeds through a radical mechanism as it is progressing smoothly in the presence of the radical initiator AIBN. Moreover, the presence of the radical was confirmed by EPR spectroscopy.⁶ Larock and co-workers described the synthesis from 2-halobenzamides and *ortho*-(trimethylsilyl)aryl triflate in the presence of a palladium catalyst.⁷ CsF is used as fluoride source to generate benzyne. A toluene–acetonitrile solvent ratio of 4:1 is important to get high yields of the desired products.

(F) *Synthesis of 3-Methylisindolin-1-ones:*

Ma and co-workers reported a CuI/L-proline-catalyzed coupling of 2-bromobenzamides with terminal alkynes to cyclize into 3-methylisindolin-1-ones. The reaction works equally well in DMF/DMSO solvents.⁸

(G) *Synthesis of Dibenzoazepinones:*

A copper-catalyzed domino reaction between 2-iodobenzamides and 2-bromophenols by using K₃PO₄ as base resulted in dibenzoxazepinones. The reaction sequence started with a copper-catalyzed Ullmann coupling followed by a base-mediated Smiles rearrangement and a final ring-closing process to give the desired product.⁹

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