Reaction Report for *DH_376*, Priority 2

Selected Position: C:1 N:23

Selected Forward Reaction: Acylation of Nitrogen Nucleophiles by Acyl/Thioacyl/Carbamoyl Halides and Analogs_N

Product

Reaction site highlighted at position C:1 N:23

Product SMILES: 0=[C:1]([n:2]1[n:3][cH:4][c:5]([C:6]([c:7]2[cH:8][cH:9][c:10]([F:11])[cH:12][cH:13]2) ([c:14]2[cH:15][cH:16][c:17]([F:18])[cH:19][cH:20]2)[0H:21])[n:22]1)[N:23]1[C@eH:24]([CH2:25][cH:27][cH:28][cH:29][cH:30][cH:31]2)[CH2:32][CH2:33][C@eH:34]([0:35][CH2:36][C:37]#[CH:38])[CH2:39]1

Proposed Transitions

Transition 1

• Forward Reaction: Acylation of Nitrogen Nucleophiles by Acyl/Thioacyl/Carbamoyl Halides and Analogs_N

• Is Chemically Valid: True

• Is Template-based: True

• **Reasoning:** This is the general template for the reaction using a carbamoyl halide electrophile, where the leaving group belongs to the class (F, Cl, Br). The reaction is plausible but may require protection of the tertiary alcohol ([OH:21]) to avoid side reactions due to its nucleophilicity.

• Is Smiles Valid: False

• Reactant 1: 0=[C:1]([F,Cl,Br])[n:2]1[n:3][cH:4][c:5]([C:6]([c:7]2[cH:8][cH:9][c:10]([F:11])[cH:12] [cH:13]2)([c:14]2[cH:15][cH:16][c:17]([F:18])[cH:19][cH:20]2)[0H:21])[n:22]1

• Reactant 2: [NH:23]1[C@H:24]([CH2:25][c:26]2[cH:27][cH:28][cH:29][cH:30][cH:31]2)[CH2:32][CH2:33] [C@H:34]([0:35][CH2:36][C:37]#[CH:38])[CH2:39]1

Reactants for Transition 1

Transition 2

• Forward Reaction: Acylation of Nitrogen Nucleophiles by Acyl/Thioacyl/Carbamoyl Halides and Analogs_N

• Is Chemically Valid: True

• Is Template-based: False

• **Reasoning:** This is a standard and common method for forming this type of carbamoyl linkage. Both reactants are synthetically accessible. The primary concern is chemoselectivity; the free tertiary alcohol ([OH:21]) on the electrophile could compete with the amine nucleophile, potentially requiring a protection strategy for the alcohol to achieve a good yield.

Is Smiles Valid: True

- Reactant 1: 0=[C:1](Cl)[n:2]1[n:3][cH:4][c:5]([C:6]([c:7]2[cH:8][cH:9][c:10]([F:11])[cH:12][cH:13]2) ([c:14]2[cH:15][cH:16][c:17]([F:18])[cH:19][cH:20]2)[OH:21])[n:22]1
- Reactant 2: [NH:23]1[C@0H:24]([CH2:25][c:26]2[cH:27][cH:28][cH:29][cH:30][cH:31]2)[CH2:32][CH2:33] [C@0H:34]([0:35][CH2:36][C:37]#[CH:38])[CH2:39]1

Reactants for Transition 2

Transition 3

• Forward Reaction: Acylation of Nitrogen Nucleophiles by Acyl/Thioacyl/Carbamoyl Halides and Analogs_N

• Is Chemically Valid: True

• Is Template-based: False

- **Reasoning:** Carbamoyl fluorides are generally more stable and less reactive than chlorides, which could improve chemoselectivity for the amine over the competing alcohol nucleophile ([OH:21]). However, they can be more difficult to prepare. This is a valid, potentially more selective, alternative to the chloride.
- Is Smiles Valid: True
- Reactant 1: 0=[C:1](F)[n:2]1[n:3][cH:4][c:5]([C:6]([c:7]2[cH:8][cH:9][c:10]([F:11])[cH:12][cH:13]2) ([c:14]2[cH:15][cH:16][c:17]([F:18])[cH:19][cH:20]2)[0H:21])[n:22]1
- Reactant 2: [NH:23]1[C@0H:24]([CH2:25][c:26]2[cH:27][cH:28][cH:29][cH:30][cH:31]2)[CH2:32][CH2:33] [C@0H:34]([0:35][CH2:36][C:37]#[CH:38])[CH2:39]1

$$\begin{array}{c} \text{HO.21} \\ \text{C.13} = \overset{\text{C.12}}{\text{C.16}} & \overset{\text{C.13}}{\text{C.16}} & \overset{\text{C.12}}{\text{C.15}} & \overset{\text{C.13}}{\text{C.20}} & \overset{\text{C.29}}{\text{C.29}} & \overset{\text{C.28}}{\text{C.27}} & \overset{\text{C.33}}{\text{C.33}} & \overset{\text{C.33}}{\text{C.36}} & \overset{\text{C.37}}{\text{C.37}} & \overset{\text{C.38}}{\text{C.36}} & \overset{\text{C.37}}{\text{C.39}} & \overset{\text{C.38}}{\text{C.36}} & \overset{\text{C.37}}{\text{C.39}} & \overset{\text{C.38}}{\text{C.39}} & \overset{\text{C.39}}{\text{C.39}} & \overset{\text{C.39}}{\text{C.3$$

R1 R2

Transition 4

• Forward Reaction: Acylation of Nitrogen Nucleophiles by Acyl/Thioacyl/Carbamoyl Halides and Analogs_N

• Is Chemically Valid: True

• Is Template-based: False

• **Reasoning:** Carbamoyl bromides are more reactive than chlorides. This increased reactivity would likely exacerbate the potential side reaction with the tertiary alcohol ([OH:21]), making chemoselectivity a significant challenge. While chemically possible, it is less practical than using the corresponding chloride or fluoride.

• Is Smiles Valid: True

• Reactant 1: 0=[C:1](Br)[n:2]1[n:3][cH:4][c:5]([C:6]([c:7]2[cH:8][cH:9][c:10]([F:11])[cH:12][cH:13]2) ([c:14]2[cH:15][cH:16][c:17]([F:18])[cH:19][cH:20]2)[OH:21])[n:22]1

• Reactant 2: [NH:23]1[C@0H:24]([CH2:25][c:26]2[cH:27][cH:28][cH:29][cH:30][cH:31]2)[CH2:32][CH2:33] [C@0H:34]([0:35][CH2:36][C:37]#[CH:38])[CH2:39]1

Reactants for Transition 4

Transition 5

• Forward Reaction: Acylation of Nitrogen Nucleophiles by Acyl/Thioacyl/Carbamoyl Halides and Analogs_N

• Is Chemically Valid: False

• Is Template-based: False

• **Reasoning:** Carbamoyl iodides are highly reactive and generally unstable, making them impractical for this transformation. The high reactivity would lead to very poor chemoselectivity with the unprotected alcohol ([OH:21]). This route is considered invalid due to the instability of the electrophile.

• Is Smiles Valid: True

- Reactant 1: 0=[C:1](I)[n:2]1[n:3][cH:4][c:5]([C:6]([c:7]2[cH:8][cH:9][c:10]([F:11])[cH:12][cH:13]2) ([c:14]2[cH:15][cH:16][c:17]([F:18])[cH:19][cH:20]2)[0H:21])[n:22]1
- Reactant 2: [NH:23]1[C@0H:24]([CH2:25][c:26]2[cH:27][cH:28][cH:29][cH:30][cH:31]2)[CH2:32][CH2:33] [C@0H:34]([0:35][CH2:36][C:37]#[CH:38])[CH2:39]1

Reactants for Transition 5

Transition 6

• Forward Reaction: Acylation of Nitrogen Nucleophiles by Acyl/Thioacyl/Carbamoyl Halides and Analogs_N

• Is Chemically Valid: True

• Is Template-based: False

• **Reasoning:** This disconnection proposes using an N-hydroxysuccinimide (NHS) activated ester as the electrophile. NHS esters are stable, isolable solids that react cleanly and selectively with amines, even in the presence of alcohols like [OH:21]. This is a very common and robust strategy, making it a highly valid option.

• Is Smiles Valid: True

• **Reactant 1:** 0=C1CC(=0)N10[C:1](=0)[n:2]1[n:3][cH:4][c:5]([C:6]([c:7]2[cH:8][cH:9][c:10]([F:11])[cH:12] [cH:13]2)([c:14]2[cH:15][cH:16][c:17]([F:18])[cH:19][cH:20]2)[0H:21])[n:22]1

• Reactant 2: [NH:23]1[C@@H:24]([CH2:25][c:26]2[cH:27][cH:28][cH:29][cH:30][cH:31]2)[CH2:32][CH2:33] [C@@H:34]([0:35][CH2:36][C:37]#[CH:38])[CH2:39]1

Reactants for Transition 6

Transition 7

• Forward Reaction: Acylation of Nitrogen Nucleophiles by Acyl/Thioacyl/Carbamoyl Halides and Analogs_N

• Is Chemically Valid: True

• Is Template-based: False

• **Reasoning:** This disconnection proposes using an N-acylimidazole as the activated electrophile. This reagent is typically prepared from a precursor and carbonyldiimidazole (CDI). It is an excellent, mild method for this transformation, known for high chemoselectivity that favors amine nucleophiles over alcohols like [OH:21]. This is a highly plausible and synthetically useful option.

• Is Smiles Valid: True

- Reactant 1: 0=[C:1]([n:2]1[n:3][cH:4][c:5]([C:6]([c:7]2[cH:8][cH:9][c:10]([F:11])[cH:12][cH:13]2) ([c:14]2[cH:15][cH:16][c:17]([F:18])[cH:19][cH:20]2)[0H:21])[n:22]1)n1cncc1
- Reactant 2: [NH:23]1[C@H:24]([CH2:25][c:26]2[cH:27][cH:28][cH:29][cH:30][cH:31]2)[CH2:32][CH2:33] [C@H:34]([0:35][CH2:36][C:37]#[CH:38])[CH2:39]1

Reactants for Transition 7