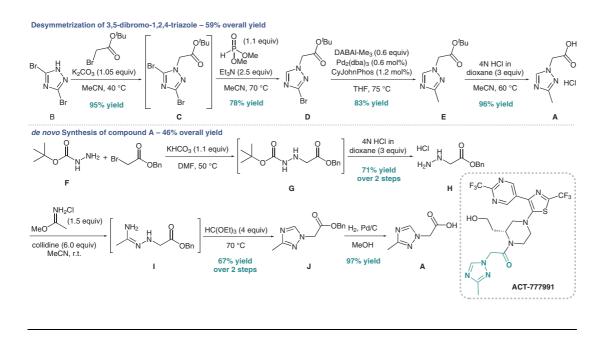
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Development of a Scalable Route toward an Alkylated 1,2,4-Triazol, a Key Starting Material for CXCR3 Antagonist ACT-777991 Org. Process Res. Dev. **2023**, 27, 928–937, DOI: 10.1021/acs.oprd.3c00051.

Conquering Regioselectivity Issues: Scalable Synthesis to an Alkylated 1,2,4-Triazole Building Block



Significance: ACT-777991 is a CXCR3 antagonist currently investigated in Phase 1 clinical trials for the treatment of type 1 diabetes which affects about 9 million people worldwide. Davenport et al. developed two scalable synthetic routes to 1,2,4triazole fragment **A** of **ACT-777991** whose initial synthesis via direct triazole alkylation suffered from poor regioselectivity control, thus providing **A** only in about 16% overall yield (not shown). Comment: The first synthetic route to A involved alkylation of symmetrical 3,5-dibromo-1,2,4-triazole (B) with tert-butyl-2-bromoacetate to yield intermediate C which was telescoped into the reduction step to selectively form intermediate **D**. Methylation of **D** was accomplished via a palladiumcatalyzed cross-coupling reaction with 1,4-diazabicyclo[2.2.2]octan-bis(trimethylaluminum) (DABAI-Me₃) as the methylating agent. Notably, save removal of DABAI-Me₃ from the end of reaction mixture containing E required a reverse quenching procedure into aqueous acidic acid to control methane off-gassing. After isolation of E, hydrolysis of the benzyl ester provided A as an HCl salt in 59% overall yield. To circumvent the use of DABAI-Me₃, a second synthesis was developed which proceeded via hydrazine HCl salt H. Slow addition of H to methylacetimidate formed condensation product I in high conversion, and a subsequent reaction with triethylorthoformate yielded benzyl ester J in 67% yield over two steps. The *de novo* synthesis provided **A** in 46% overall yield and was shown to be in the most cost-effective.

Category

Innovative Drug Discovery and Development

Key words

CXCR3 inhibitors

1,2,4-triazoles

DABAI-Me₃

process safety

of the Month

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