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A NOVEL SYNTHESIS OF 1, 2-DIARYL-2, 2-DIFLUOROETHANONES

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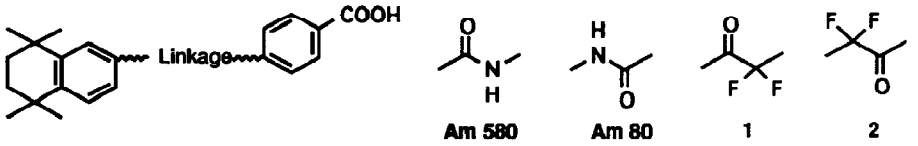
Abstract. A novel procedure for the synthesis of 1, 2-diaryl-2, 2-difluoroethanones involving Stille reaction of an aryl difluoroacetyl chloride and an arylstannane has been developed. Application of this procedure for the preparation of two retinoids is described.

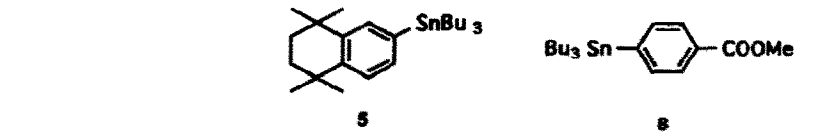
Retinoic acid has been shown to play an important role in many physiological activities. Cumulative evidence has indicated that retinoic acid and its derivatives (retinoids) may exert their functions by regulating gene expression mediated by two classes of nuclear receptors: RARs (α, β, γ) and RXRs (α, β, γ).[1] In attempts to elucidate the function of each receptor, several receptor selective retinoids have been reported. Among these retinoids, **Am 580** and **Am 80** were found to be RAR α selective.[2] As part of our program, we were interested in preparing difluoroketone derivatives **1** and **2** to investigate the importance of the amide linkage in the interactions of the retinoids with the receptors.



Am 580 **Am 80** **1** **2**

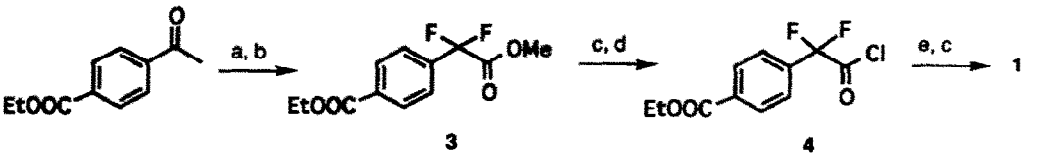
Although several approaches have been developed to prepare 1, 2 -diaryl-2, 2-difluoroethanones, these procedures are either limited to the 1,2-diaryl 2, 2-difluoroethanones in which the two aryl substituents are the same, or require inconvenient procedures.[3] Hamer and his colleagues have prepared diaryl 2, 2-difluoroketones by displacing a chlorodifluoromethyl aryl ketone with an aryl lithium.[3a] However, attempts to utilize this approach to prepare **1** gave undesired addition rather than the displacement product.

In a different approach, diaryl difluoroketones **1** and **2** were constructed by Stille reaction of a difluoroacetyl chloride with an arylstannane (Schemes I and II). Ethyl *p*-acetylbenzoate was first oxidized with SeO_2,[4] followed by addition of diazomethane to give an α-keto methyl ester which was treated with DAST[5] to yield difluoroester **3** (Scheme I). This activated α-difluoro ester was selectively hydrolyzed at room temperature and the resulting acid was converted to acid chloride **4**. Stille reaction of **4** with stannane **5**[6] in the presence of catalytic $BnPd(PPh_3)_2Cl$ in HMPA[7] followed by saponification of the ester provided difluoroketone acid **1**. In a similar approach, **7** was prepared from 1, 1, 4, 4-tetramethyl-1, 2, 3, 4-tetrahydronaphthalene shown in Scheme II. The difluoroacetyl chloride was coupled to stannane **8** and hydrolysis of the ester yielded retinoid **2**. In the RAR transactivation assays,[8] **1** and **2** do not show activity or selectivity that is better than **Am 80** or **Am 580**.

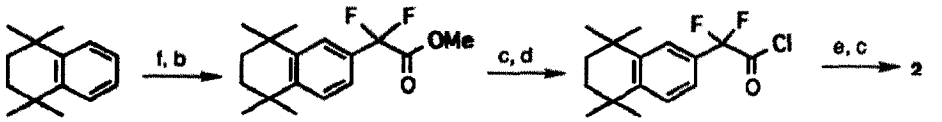


5 8

Scheme I



Scheme II



reagents: a) SeO_2-pyridine; CH_2N_2 (49%); b) DAST (75-95%); c) NaOH; d) $(COCl)_2$, DMF; e) **5** or **8**, $BnPd(PPh_3)_2Cl$ (56-74%); f) $ClCOCOOMe\text{-}AlCl_3$ (60%).

In conclusion, the easily prepared starting materials and the mild conditions of the Stille coupling reaction described above should provide a novel approach for the synthesis of a variety of different 1, 2-diaryl-2, 2-difluoroethanones.

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