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Synthesis of novel 1,4,5-trisubstituted 3-trifluoromethylpyrazoles via microwave-assisted Stille coupling reactions

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Abstract

1,5-Disubstituted 3-trifluoromethylpyrazoles were reacted with *N*-bromosuccinimide in DMF at room temperature or 70–80 °C for 1–2 h to afford the corresponding 4-bromo-substituted pyrazoles **2** in 95–99% yields. The microwave-assisted Stille coupling reactions of **2** with arylstannanes having a substituent on the benzene ring and allylstannane in refluxing CH_3CN in the presence of $Pd(PPh_3)_4$ provided the corresponding 1,4,5-trisubstituted 3-trifluoromethylpyrazoles **3** in 75–98% yields.

Keywords: Bromination; 1,5-Disubstituted 3-trifluoromethylpyrazoles; Arylstannanes; Allystannane; Microwave-assisted Stille coupling reactions; 1,4,5-Trisubstituted 3-trifluoromethylpyrazoles

1. Introduction

The pyrazole ring has been known as an important framework in a large number of compounds possessing pharmaceutical and agrochemical properties [1–6]. Numerous methods for the synthesis of this family of compounds have been well documented in the previous literatures [7–15], but methods are mostly related to the synthesis of nonfluorinated pyrazoles. However, to our knowledge, there have been limited methodologies for the preparation of trifluoromethylated pyrazoles. Since the introduction of a trifluoromethyl group into the pyrazole ring system has often increased the biological properties [16,17], many efforts have been devoted to the development of synthetic methodologies for the preparation of trifluoromethylated pyrazoles. General methods for the preparation of these compounds involve the reactions of hydrazine derivatives with trifluoromethylated precursors such as 1-trifluoromethylated 1,3-diketones [16,18,19], trifluoromethylacetylenic esters [20], pentafluoroethylacetylenes [21], trifluoroacetyl acetylenes [22], β-alkoxyvinyl trifluoromethyl ketones [23,24], β-trifluoromethyl enaminones [25,26], *N*-aryl-1-trifluoromethyl acetylenic imines [27] and 1-pentafluoroethyl-2-iodoalkenes [28,29]. 1,3-Dipolar cycloaddition reaction of 2-bromo-3,3,3-trifluoropropene with diazomethane followed by dehydration also afforded the corresponding 3-trifluoromethylpyrazole [30]. Recently, a direct preparation of 5-tributylstannyl-4-trifluoromethylpyrazole was accomplished by 1,3-dipolar cycloaddition reaction of tributyl(3,3,3-trifluoro-1-propynyl)stannane with diazomethane [31,32]. Dipolarophiles such as phenylacetylene, vinylsulfone and 2-bromoacrylate were also reacted with trifluoroacetyltriphenylsilane 2,4,6-triisopropylbenzenesulfonyl hydrazone to give the corresponding 3-trifluoromethylpyrazoles [33]. However, the most of these methods focused on the preparation of mono- and disubstituted trifluoromethylpyrazole derivatives. In spite of importance of trisubstituted trifluoromethylpyrazole in recent years, the methods for the preparation of trisubstituted trifluoromethylpyrazoles have been quite limited in the previous literatures [16,34–36]. Moreover, these methods have some drawbacks such as a lack of generality and uneasy availability of starting materials. Herein, we wish to report a novel and general approach to 1,4,5-trisubstituted 3-trifluoromethylpyrazoles via the microwave-assisted Stille coupling reactions of the corresponding 1,5-disubstituted 4-bromo-3-trifluoromethylpyrazoles with arylstannanes or allylstannane in the presence of palladium catalyst.

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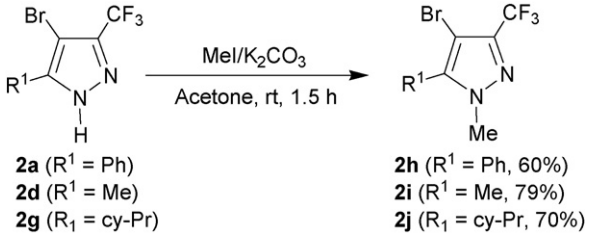
2. Results and discussion

The starting materials, 1,5-disubstituted 3-trifluoromethylpyrazoles **1a–f**, were prepared in 92–98% isolated yields from the condensation reaction of 1-trifluoromethylated 1,3-dicarbonyl compounds with hydrazine derivatives in 1,4-dioxane, except for methylhydrazine, followed by dehydration reaction in refluxing toluene. Small quantities of undesired regioisomer, 1,3-disubstituted 5-trifluoromethylpyrazoles, were separated by column chromatographic purification. A recent study has established that this high regioselectivity was due to electron-withdrawing group such as CF_3 on C-1 of 1,3-dicarbonyl compounds [37]. In order to install the aryl or allyl substitutent onto the 4-position of fully assembled pyrazoles **1**, we chose to explore a carbon–carbon bond-forming reaction in the presence of transition-metal catalysis. Therefore, we carried out the bromination reaction with the corresponding bromo succinimide to introduce a bromo substituent as a reacting site of the coupling reaction. We found 1,5-disubstituted 4-bromo-3-trifluoromethylpyrazoles **2a–g** were prepared in 95–99% isolated yields from the reaction of **1** with *N*-bromosuccinimide in DMF at room temperature or 70–80 °C. The results of these reactions were summarized in Table 1. The use of other solvents such as CH_2Cl_2, CCl_4 or CH_3CN in this bromination reaction caused not only to retard the reaction, but also to decrease the yield of **2**. The previous method using sodium acetate and bromine did not provide a satisfied result for the formation of **2** [38].

Since 5-substituted 3-trifluoromethyl-1-methylpyrazoles were not directly synthesized from the reaction of 1-trifluoromethylated 1,3-dicarbonyl compounds with methylhydrizine, 5-substituted 4-bromo-3-trifluoromethyl-1-methylpyrazoles **2h–j** were prepared regiospecifically from the methylation reaction of **2a**, **2d** and **2g** with methyl iodide in the presence of K_2CO_3 (Scheme 1). The assignment of regioisomers **2h–j** was based on ^{1}H NMR chemical shifts. The ^{1}H NMR spectrum of **2h–j** showed that the peaks of *N*-methyl protons appeared at δ = 3.84–3.95 ppm which is consistent with the range of chemical shift of a similar structure, 4-substituted

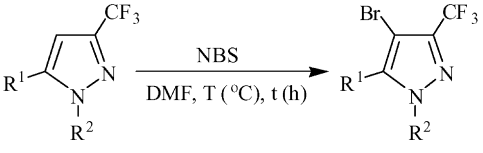


Scheme 1.

3-trifluoromethyl-1-methylpyrazoles [39]. The resonance of *N*-methyl protons of regioisomer, 4-substituted 5-trifluoromethyl-1-methylpyrazoles, appeared at δ = 4.07–4.11 ppm. Regiospecificity on *N*-methylation of **2a**, **2d** and **2g** to give 5-substituted 4-bromo-3-trifluoromethyl-1-methylpyrazole **2h–j** can be explained by the steric effect of trifluoromethyl group in the formation of regioisomer, 3-substituted 4-bromo-5-trifluoromethyl-1-methylpyrazole. A similar result was established in the formation of 1-methyl-3-trimethylsilylpyrazole and 1-methyl-3,4-bis(trimethylsilyl)pyrazole [40].

Although several previous literature reports described the coupling reactions, such as Suzuki, Stille, and Sonogashira couplings, performed on nonfluorinated 5-bromopyrazoles [10,41] and pyrazole triflates [42], there has been only one example (Sonogashira reaction) in the coupling reactions on trifluoromethylated halopyrazoles [38]. Among the coupling reactions, we investigated Stille coupling reaction of **2** with arylstannane or allylstannane. We carried out the cross-coupling reaction of **2c** with phenylstannane as a standard reaction to find out an optimized reaction condition. When **2c** was reacted with phenylstannane in the presence of $Pd(PPh_3)_4$ (5 mol%) at refluxing CH_3CN for 24 h, the cross-coupled product **3a** was obtained in 76% isolated yield based on the only 15% conversion of the starting material. The use of DMF as a solvent under the same reaction condition caused to enhance the conversion of the starting material up to 40%, but reaction was still sluggish. Recently, we reported that microwave-assisted cross-coupling reaction of trifluoromethylated chloropyrimidines with arylstannanes afforded the corresponding coupled product in high yields [43]. We applied this reaction condition to explore the coupling reaction of **2** with arylstannane or allylstannane. It was found that microwave-assisted coupling reaction of **2c** with phenylstannane in CH_3CN at 180 °C for 1 h afforded the coupled product **3a** in 97% isolated yield based on the 100% conversion of **2c**. The arylstannane having a substituent on the benzene ring and allylstannane also underwent the coupling reactions with **2c** to give **3b–e** in 92–98% isolated yields under the same reaction condition. The reactions between **2b** and arylstannane also afforded the corresponding coupled products **3f–i** in 91–92% isolated yields, but the reactions were more sluggish than that of **2c** with phenylstannane and a prolong reaction time (1.5 h) was required. A small amount of reduced product was obtained in less than 5% yield for each case. The reaction of **2b** with allylstannane under the same reaction condition afforded the corresponding coupled product **3j** in 97% isolated yield. Similarly, **2g** underwent the coupling reaction with

Table 1
Preparation of 1,5-disubstituted 4-bromo-3-trifluoromethylpyrazoles **2**



1 **2**

Compound no.	R^1	R^2	*T* (°C)	*t* (h)	Yield (%)[a]
2a	Ph	H	70–80	2	96
2b	Ph	$PhCH_2$	70–80	2	98
2c	Ph	Ph	70–80	2	99
2d	Me	H	25	1	99
2e	Me	$PhCH_2$	25	1	95
2f	cy-Pr	Ph	25	1	98
2g	cy-Pr	H	25	1	99

[a] lsolated yield.