One-Pot Three-Component Synthesis of Tetrasubstituted N—H Pyrroles from Secondary Propargylic Alcohols, 1,3-Dicarbonyl Compounds and *tert*-Butyl Carbamate

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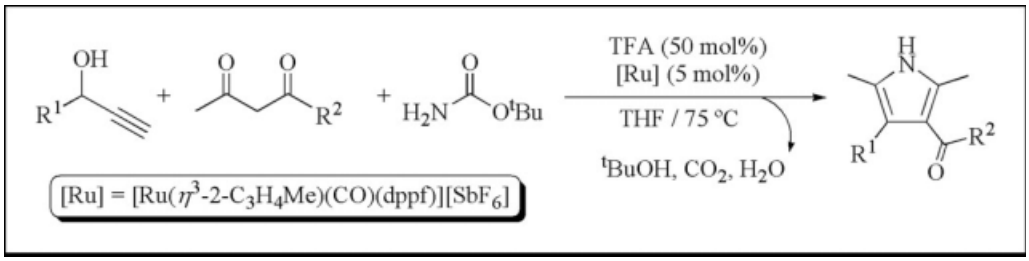

Several tetrasubstituted N—H pyrroles, functionalized with ester or ketone groups at C-3 position, were prepared by one-pot coupling of secondary propargylic alcohols with 1,3-dicarbonyl compounds and *tert*-butyl carbamate, *via in situ* deprotection of the corresponding pentasubstituted N-Boc pyrroles. The three-component coupling process was promoted by the combined use of the 16-electron ruthenium(II) catalyst [Ru(η^3-2-C_3H_4Me)(CO)(dppf)][SbF_6] (dppf = 1,1′-bis(diphenylphosphino)ferrocene) and trifluoroacetic acid (TFA).

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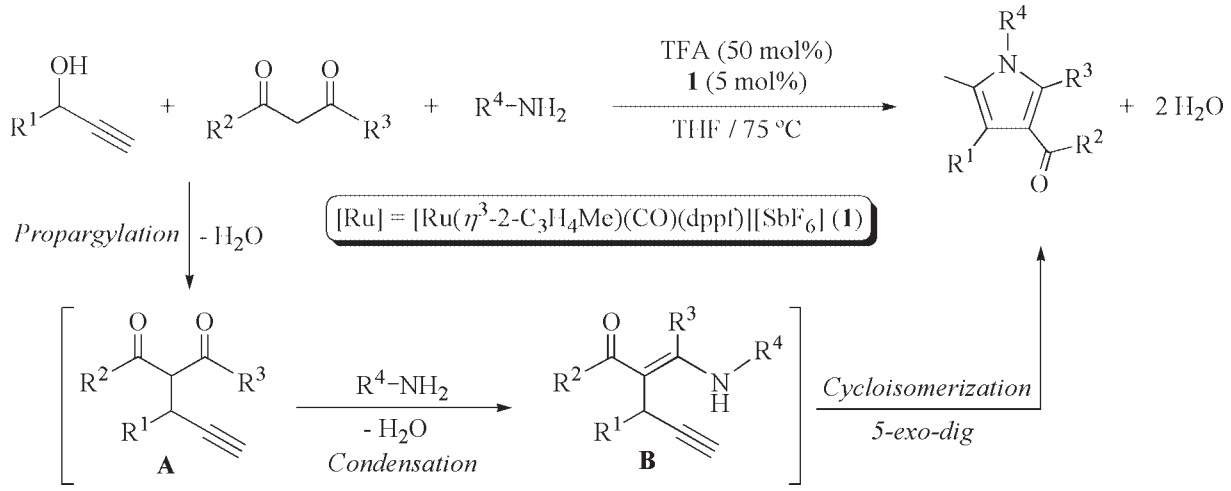
INTRODUCTION

Pyrroles are one of the most prominent heterocyclic compounds, being present as key structural motifs in several natural products (for reviews, see [1]), conducting organic materials (for reviews, see [2]), and bioactive molecules (for reviews, see [3]). Consequently, a large number of general methods have been developed to construct these five-membered heterocycles, including the well-known Knorr, Paal-Knorr, and Hantzch syntheses, 1,3-dipolar cycloaddition reactions, reductive couplings, and aza-Wittig reactions (see, for example, [4]). However, it is still challenging to prepare polysubstituted pyrroles directly from inexpensive and readily available starting materials. In this sense, important efforts have been made during the last years in the design of multicomponent strategies (for reviews and highlights on pyrrole syntheses through multicomponent reactions, see [5] and for recent examples of multicomponent syntheses of pyrroles, see [6]). Multicomponent reactions (MCR), in which multiple reactants are combined into a single product, offer significant advantages over classical linear syntheses since molecular diversity can be reached from simple precursors in an efficient, economic, and environmentally friendly manner (see, for example, [7]).

In this context, we have recently described an efficient one-pot three-component coupling reaction for the synthesis of fully substituted pyrroles from secondary propargylic alcohols, 1,3-dicarbonyl compounds (β-diketones or β-keto esters), and primary amines (Scheme 1) [8]. The process, which is catalyzed by the 16-electron allyl-ruthenium(II) complex [Ru(η^3-2-C_3H_4Me)(CO)(dppf)][SbF_6] (**1**; dppf = 1,1′-bis(diphenylphosphino)ferrocene) and trifluoroacetic acid (TFA), involves the initial propargylation of the 1,3-dicarbonyl compound promoted by TFA, subsequent condensation between the resulting γ-keto alkyne **A** and the primary amine to afford a β-enamino ester or ketone **B**, which undergoes a ruthenium-catalyzed 5-*exo-dig* annulation to give the final pyrrole (indium(III) chloride is also able to promote efficiently these propargylation/condensation/cycloisomerization tandem reactions [9]; we note that involvement of propargylic alcohols in multicomponent syntheses of pyrroles is scarcely documented [10]).

Following this route, which allows the direct introduction of carbonyl functionalities onto the pyrrolic skeleton and tolerates the presence of a wide variety of functional groups in the starting materials, a large number of pentasubstituted pyrroles could be synthesized in good to excellent yields [8]. As an extension of these studies, herein, we report on the applicability of this one-pot

Scheme 1



three-component reaction for the synthesis of tetrasubstituted N—H pyrroles.

RESULTS AND DISCUSSION

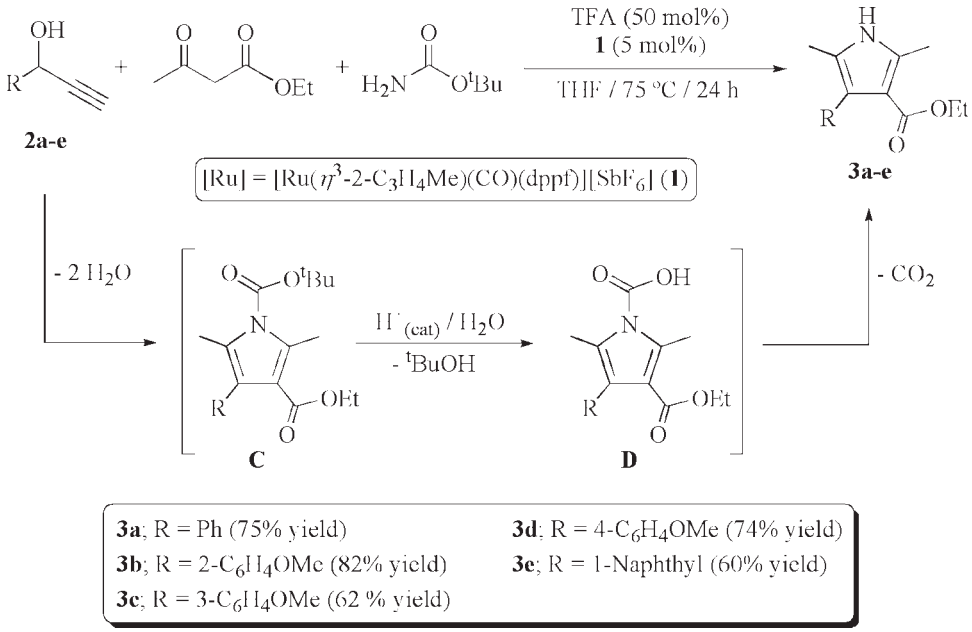
In our first report, we already attempted the preparation of N—H pyrroles by coupling secondary propargylic alcohols with 1,3-dicarbonyl compounds in the presence of simple ammonia sources such as NH_4OH or NH_4Cl. Unfortunately, the desired products were not formed using these inexpensive reagents, the reactions leading instead to the major formation of tetrasubtituted furans as the result of the known 5-*exo-dig* annulation of γ-keto alkyne intermediates **A** [11]. Only the use of propargylamine allowed us the preparation of this type of molecules (one example), *via* TFA-promoted scission of the C—N bond on the initially formed pentasubstituted *N*-propargyl pyrrole [8]. However, an extremely long reaction time (4 days) was required reducing considerably the synthetic interest of the process. This fact prompted us to search for a more appropriate NH source compatible with the propargylation/condensation/cycloisomerization sequence outlined in Scheme 1. Thus, our attention turned firstly to ammonium carbamate since it was successfully employed by Zhan and coworkers in related reactions using $InCl_3$ as promoter [9]. However, the reactions, which were performed in the presence of variable amounts of this reagent (1–10 equiv.), led again to the major formation of furans with only traces of the desired NH pyrroles being detected by GC/MS in the crude reaction mixtures. Neither the use of primary silylamines, such as NH_2SiPh_3, gave to the desired results. Finally, we were pleased to find that commercially available *tert*-butyl carbamate is compatible with our one-pot three-component reaction. Thus, as shown in Scheme 2, treatment of THF solutions of propargylic alcohols **2a–e** with ethyl acetoacetate and *tert*-butyl carbamate (1:1:1 molar ratio) in the presence of 50 mol % of TFA and 5 mol % of complex **1** led, after 24 h of heating (75°C), to the selective formation of pyrroles **3a–e**, which were isolated in 60–82% yield after appropriate chromatographic workup.

Characterization of **3a–e** was straightforward by following their analytical and spectroscopic data. In particular, the presence of the N—H unit was unambiguously confirmed by the appearance of: (i) an intense absorption band at about 3300 cm^{-1} in their IR spectra, and (ii) a singlet signal at about 8 ppm in their ^{1}H-NMR spectra. Pyrroles **3a–e** result from the TFA-mediated hydrolysis of the *tert*-butyl ester (Boc) group in the initially formed pentasubstituted pyrroles **C** (detected monitoring the reactions by GC/MS) and subsequent decarboxylation of the resulting intermediates **D** (The Boc group is a versatile and commonly used protecting group for the pyrrole nitrogen atom, being easily removable in acidic media. See, for example, [12]).

Following the same approach, NH-pyrroles **4a–d** and **5a–b** (Fig. 1) could also be synthesized in 64–79% yield employing methyl acetoacetate and 2,4-pentanedione as the 1,3-dicarbonyl compound, respectively, thus confirming the generality of this transformation.

In summary, an efficient MCR reaction for the preparation of tetrasubstituted N—H pyrroles, functionalized with carbonyl groups at C-3 position, has been developed using the catalytic system [Ru(η^3-2-C_3H_4Me)(CO)(dppf)][SbF_6]/TFA. The results reported herein represent a new example of the utility of the allyl-ruthenium(II) complex **1** in synthetic organic chemistry (for an account on the applications of complex **1** in synthesis, see [13]).

Scheme 2



3a; R = Ph (75% yield)
3b; R = 2-C_6H_4OMe (82% yield)
3c; R = 3-C_6H_4OMe (62 % yield)
3d; R = 4-C_6H_4OMe (74% yield)
3e; R = 1-Naphthyl (60% yield)

EXPERIMENTAL

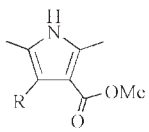
Infrared spectra were recorded on a Perkin-Elmer 1720-XFT spectrometer. NMR spectra were recorded on a Bruker DPX-300 instrument at 300 MHz (^{1}H) or 75 MHz (^{13}C). The chemical shift values (δ) are given in parts per million and are referred to the residual peak of the deuterated solvent used ($CDCl_3$). DEPT experiments have been carried out for all the compounds reported. GC/MS measurements were performed on a Agilent 6890N equipment coupled to a 5973 mass detector (70 eV electron impact ionization) using a HP-1MS column. Elemental analyses were acquired with a Perkin-Elmer 2400 microanalyzer. Flash chromatography was performed using Merck silica gel 60 (230–400 mesh). All reagents were obtained from commercial suppliers and used without any further purification, with the exception of complex **1** [14] and propargylic alcohols **2b–e** [15] which were prepared by following the methods reported in the literature.

General procedure for the catalytic reactions. The appropriate propargylic alcohol **2a–e** (1 mmol), 1,3-dicarbonyl compound (1 mmol), and *tert*-butyl carbamate (1 mmol) were introduced into a sealed tube under a nitrogen atmosphere. THF (0.5 mL), complex **1** (0.049 g, 0.05 mmol), and TFA (37 μL, 0.5 mmol) were then added at room temperature, and the resulting solution was heated at 75°C for 24 h. After elimination of the solvent under reduced pressure, the crude reaction mixture was purified by column chromatography over silica gel using an ethyl acetate/hexane mixture (1:10 v/v) as eluent. ^{1}H and ^{13}C{^{1}H} NMR spectra, as well as melting points, obtained for compounds **3a** [9], **3b** [16], **3d** [8], **3e** [9], **4a** [16], **4c** [16], **5a** [17], and **5b** [18] were in complete accord with those described in the literature. Characterization data for the novel pyrroles **3c** and **4b**,**d** are as follows:

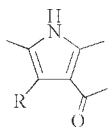
4-(3-Methoxyphenyl)-2,5-dimethyl-1H-pyrrole-3-carboxylic acid ethyl ester (3c) Orange solid; Yield: 0.169 g (62%); mp: 144°C; IR (Nujol): 3311 (N—H), 1683 (C=O) cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.08 (t, J = 7.1 Hz, 3H), 2.10, 2.49, and 3.80 (s, 3H each), 4.09 (q, J = 7.1 Hz, 2H), 6.78–6.86 (m, 3H), 7.24 (m, 1H), 8.21 (s, 1H) ppm; ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 11.1, 13.5, 14.0, 55.1, 59.0, 110.5, 111.3, 116.0, 122.1, 123.0, 123.5, 128.1, 133.5, 137.6, 158.7, 165.7 ppm; GC-MS (EI, 70 eV): *m*/*z* 273 (100%, M$^+$), 244 (60), 227 (55), 198 (18), 184 (25), 168 (20), 156 (15), 115 (15); Anal. Calcd. for $C_{16}H_{19}O_3N$: C, 70.31; H, 7.01; N, 5.12. Found: C, 70.44; H, 7.19; N, 5.06.

4-(2-Methoxyphenyl)-2,5-dimethyl-1H-pyrrole-3-carboxylic acid methyl ester (4b) Orange solid; Yield: 0.205 g (79%); mp: 138°C; IR (Nujol): 3314 (N—H), 1683 (C=O) cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.05, 2.47, 3.59, and 3.75 (s, 3H each), 6.90–6.99 (m, 2H), 7.15 (dd, J = 7.4 and 1.7 Hz, 1H), 7.26 (td, J = 8.0 and 1.7 Hz, 1H), 8.31 (s, 1H) ppm; ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 11.1, 13.4, 50.3, 55.3, 110.3, 111.1, 117.7, 119.9, 123.8, 125.2, 127.6, 131.5, 133.6, 157.4, 166.4 ppm; GC-MS (EI, 70 eV): *m*/*z* 259 (85%, M$^+$), 228 (15), 212 (100), 200 (50), 184 (60), 168 (18), 154 (15), 128 (35), 115 (45), 15 (90); Anal. Calcd. for $C_{15}H_{17}O_3N$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.55; H, 6.74; N, 5.52.

4-(4-Methoxyphenyl)-2,5-dimethyl-1H-pyrrole-3-carboxylic acid methyl ester (4d) Orange solid; Yield: 0.199 g (77%);



4a; R = Ph (68% yield)
4b; R = 2-C_6H_4OMe (79% yield)
4c; R = 3-C_6H_4OMe (64 % yield)
4d; R = 4-C_6H_4OMe (77% yield)



5a; R = Ph (70% yield)
5b; R = 2-C_6H_4OMe (73% yield)

Figure 1. Structures of the NH-pyrroles **4a–d** and **5a–b**.

mp: 140°C; IR (Nujol): 3295 (N—H), 1687 (C=O) cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.08, 2.48, 3.64, and 3.82 (s, 3H each), 6.89 and 7.18 (d, J = 8.6 Hz, 2H each), 8.15 (s, 1H) ppm; $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 11.1, 13.7, 50.3, 55.1, 110.1, 112.8, 122.0, 123.4, 128.4, 131.2, 133.9, 157.7, 166.3 ppm; GC-MS (EI, 70 eV): m/z 259 (100%, M^+), 244 (20), 228 (20), 198 (18), 184 (23), 168 (24), 156 (30), 115 (40), 42 (60), 15 (80); Anal. Calcd. for $C_{15}H_{17}O_3N$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.31; H, 6.78; N, 5.59.

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