A Novel Synthesis of Tetrasubstituted Pyrroles via Tandem Benzylic Oxidative Cyclization

Issa Yavari,* Mohammad J. Bayat

Chemistry Department, Tarbiat Modares University, PO Box 14115-175, Tehran, Iran
Fax +98(21)88006544; E-mail: yavarisa@modares.ac.ir

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Abstract: A new method for the synthesis of tetrasubstituted pyrroles from a domino reaction between primary benzylamines and dialkyl acetylenedicarboxylates, in the presence of potassium cyanide without using a metal or oxidant, is described.

Key words: pyrrole, acetylenic ester, primary benzylamine, potassium cyanide

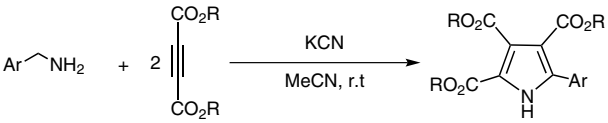
Sequential multiple-bond-forming transformations, which include tandem reactions, are of interest in the development of synthetic organic chemistry.[1,2] Carbon–carbon and carbon–heteroatom bond formation through C–H bond functionalization is another important strategy in organic synthesis.[3–5] Herein, a new method for the synthesis of tetrasubstituted pyrroles via tandem benzylic oxidative cyclization without using any metal or oxidant is described. The pyrrole ring system is present in a large number of natural products and pharmaceuticals and materials having desirable properties.[6–11] Although there are many reports for the synthesis of pyrroles,[12–17] the number of methods for synthesizing substituted pyrroles through benzylic oxidative cyclization is limited.[18] In recent years, several reports of benzylic C–H functionalization have been published.[18–28]

As part of our current studies on the development of new multicomponenent reactions to synthesize novel functional heterocycles,[29–32] we herein report a domino reaction between primary benzylamines and dialkyl acetylenedicarboxylates, in the presence of potassium cyanide for the synthesis of tetrasubstituted pyrroles. This work is an extension of our recent report that the reaction between benzylamine (1 mmol) and dialkyl acetylenedicarboxylates (2 mmol) in the presence of *N*-methylimidazole (0.05 mmol) as an organocatalyst gives trialkyl 1-benzyl-6-oxo-1,6-dihydro-2,3,4-pyridinetricarboxylates in good yields.[33]

Initially, the reaction between 4-methylbenzylamine (**1b**, 1 mmol) and dimethyl acetylenedicarboxylate (**2a**, DMAD, 2 mmol) in the presence of potassium cyanide (1 mmol) was examined. The reaction proceeded smoothly and afforded trimethyl 5-(4-methylphenyl)-1*H*-pyrrole-2,3,4-tricarboxylate (**3b**) in 66% yield. In an attempt to optimize the reaction, the reaction was carried out in the presence of different amounts of KCN in MeCN, and the best result was obtained with one equivalent of KCN. Subsequently, the reaction was tested in other solvents such as dichloromethane (52% yield), *N,N*-dimethylformamide (40% yield), polyethylene glycol (50% yield), and a mixture of H_2O–MeCN (1:1, 58% yield) at room temperature, and the best result was obtained in MeCN (66% yield).

The generality of this transformation was demonstrated by applying various primary benzylamines **1** and acetylenic esters **2** under optimized conditions (1 equiv of KCN, MeCN, 24 h), and the results are summarized in Table 1. The structures of compounds **3a–j** were verified by ^{1}H NMR, ^{13}C NMR, and IR spectroscopic and mass spectrometric analysis.[34]

Table 1 Synthesis of Compounds **3a–j** from the Reaction of Benzylamines and Acetylenic Esters in the Presence of KCN[a]



1 2 3

Amine **1**	Ar	Acetylenic ester **2**	R	Product **3**	Yield (%)[b]
1a	Bn	**2a**	Me	**3a**	61
1b	4-Me$C_6H_4CH_2$	**2a**	Me	**3b**	66
1c	4-MeO$C_6H_4CH_2$	**2a**	Me	**3c**	63
1d	2-Cl$C_6H_4CH_2$	**2a**	Me	**3d**	59
1e	4-Cl$C_6H_4CH_2$	**2a**	Me	**3e**	57
1f	1-naphthyl	**2a**	Me	**3f**	51
1a	Bn	**2b**	Et	**3g**	54
1b	4-Me$C_6H_4CH_2$	**2b**	Et	**3h**	56
1c	4-MeO$C_6H_4CH_2$	**2b**	Et	**3i**	49
1f	1-naphthyl	**2b**	Et	**3j**	45

[a] Reaction conditions: benzylamines **1** (1 mmol), acetylenic ester **2**, (2 mmol), KCN (1 mmol), and MeCN (5 mL).
[b] Yield of isolated pure product after column chromatography.

A possible mechanism for this transformation is outlined in Scheme 1. The initial event involves protonation of the zwitterionic intermediate **6**, formed from KCN and **2** by

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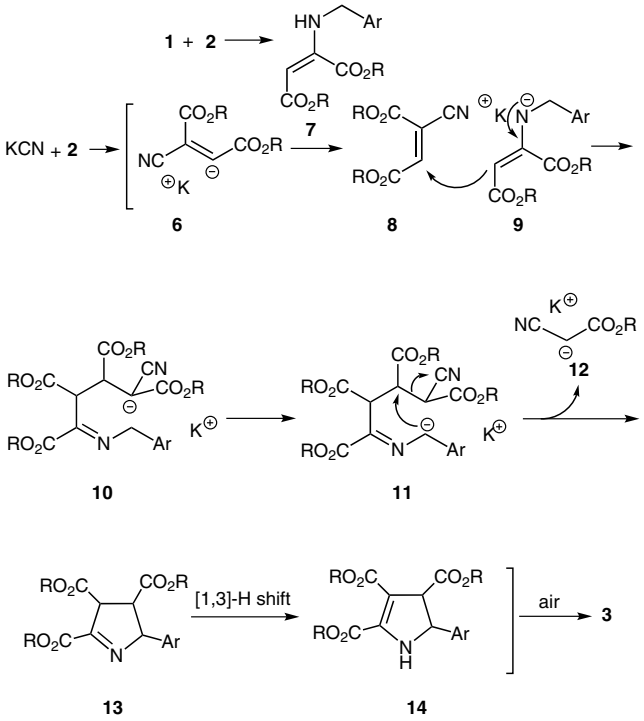
the enaminoester intermediate **7**, which itself is generated in situ from the primary amine **1** and acetylenic ester **2**, to produce intermediates **8** and **9**. Then, nucleophilic attack of the conjugate base **9** on intermediate **8** leads to adduct **10**, which undergoes intramolecular proton-transfer reactions to afford **11**. Intermediate **11** undergoes intramolecular cyclization[28] by elimination of salt **12** to generate **13**, which is converted into the desired product **3** by a formal [1,3]-H shift and air oxidation.



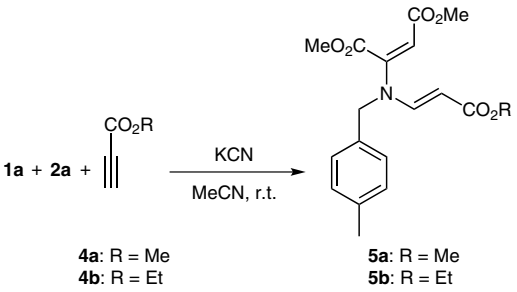
Scheme 1 A plausible mechanism for the formation of compounds **3**

The same reaction was tested using aliphatic amines such as butylamine or allylamine instead of benzylamines, but no tetrasubstituted pyrroles were detected in the reaction mixtures. The reaction of propargylamine with DMAD afforded pyrrole derivatives.[35]

To extend our knowledge of this transformation, we performed the same reaction with equimolar amounts of 4-methylbenzylamine (**1b**), DMAD, and alkyl propiolates **4**. These reactions led to the formation of dimethyl 2-{*N*-[(*E*)-2-(alkoxycarbonyl)vinyl]-*N*-benzylamino}maleates **5** in good yields (Scheme 2). This reaction afforded only the *E* isomer of **5**, as evidenced from the $^3J_{HH}$ value of about 13.3 Hz for the vicinal olefinic protons. Compounds **5** were again fully characterized with their IR, ^{1}H NMR, and ^{13}C NMR spectra.[34]

In conclusion, we have designed a new strategy for the syntheses of tetrasubstituted pyrroles using a tandem three-component reaction between benzylamines and acetylenic esters.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.



Scheme 2 Synthesis of compounds **5**

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(34) **General Procedure for the Synthesis of Compounds 3**
To a stirred solution of amine **1** (1 mmol) and acetylenic ester **2** (2 mmol) in MeCN (5 mL) was added KCN (1 mmol) at r.t. After completion of the reaction [about 24 h; TLC (EtOAc–hexane, 1:5) monitoring], the solvent was evaporated, and the residue was purified by column chromatography [silica gel (230–400 mesh; Merck); EtOAc–hexane, 1:5] to give pure product.
Trimethyl 5-Phenyl-1*H*-pyrrole-2,3,4-tricarboxylate (3a)
Pale yellow oil; yield 0.19 g (61%). IR (KBr): 3421, 3000, 1728, 1610 cm^{-1}. ^1H NMR (500.1 MHz, $CDCl_3$): δ = 3.76, 3.79, 4.04 (9 H, s, 3 MeO), 7.45–7.47 (3 H, m, CH), 7.06 (2 H, d, ^3J = 7.8 Hz, CH), 9.24 (1 H, br s, NH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 51.5, 52.3, 52.7 (3 MeO), 122.4 (C), 126.3 (C), 128.3 (2 CH), 128.6 (C), 129.9 (2 CH), 129.6 (CH), 131.9 (C), 142.6 (C), 161.7 (C=O), 164.9 (C=O), 167.8 (C=O) ppm. MS (EI): *m*/*z* (%) = 317 (3) [M^+], 302 (4), 258 (23), 91 (14), 77 (6), 59 (7). Anal. Calcd for $C_{16}H_{15}NO_6$ (317.29): C, 60.57; H, 4.56; N, 4.41. Found: C, 60. 75; H, 4.52; N, 4.47.

General Procedure for the Synthesis of Compounds 5
To a stirred solution of 4-methylbenzylamine (**1b**, 1 mmol), DMAD (1 mmol), and methyl propiolate (**4a**, 1 mmol) in MeCN (5 mL) was added KCN (1 mmol) at r.t. After completion of the reaction [about 24 h; TLC (EtOAc–hexane, 1:5) monitoring], the solvent was evaporated, and the residue was purified by column chromatography [silica gel (230–400 mesh; Merck); EtOAc–hexane, 1:5] to give pure product.
Dimethyl 2-{[(*E*)-3-Methoxy-3-oxoprop-1-enyl](4-methylbenzyl)amino}maleate (5a)
Pale yellow powder; mp 94–96 °C; yield 0.22 g (63%). IR (KBr): 3415, 2952, 1712, 1590 cm^{-1}. ^1H NMR (500.1 MHz, $CDCl_3$): δ = 2.36 (3 H, s, Me), 3.62, 3.67, 4.02 (9 H, s, MeO), 4.83 (2 H, s, CH_2N), 5.17 (1 H, d, ^3J = 13.3 Hz, CH), 5.24 (1 H, s, CH), 7.03 (2 H, d, ^3J = 7.8 Hz, CH), 7.16 (2 H, t, ^3J = 7.8 Hz, CH), 7.59 (2 H, t, ^3J = 13.3 Hz, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 21.0 (Me), 51.1 (CH_2N), 51.5, 51.6, 53.4 (3 MeO), 97.1 (CH), 98.8 (CH), 125.7 (2 CH), 129.8 (2 CH), 130.0 (C), 137.7 (C), 143.4 (CH), 150.1 (C), 164.4 (C=O), 166.2 (C=O), 167.5 (C=O) ppm. MS (EI): *m*/*z* (%) = 347 (3) [M^+], 332 (8), 288 (11), 105 (25), 77 (13), 59 (7). Anal. Calcd for $C_{18}H_{21}NO_6$ (347.36): C, 62.24; H, 6.09; N, 4.03. Found: C, 62.51; H, 6.14; N, 4.08.
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