Approach to Trisubstituted 1*H*-Pyrroles from Alkynoates and Amines Mediated by *tert*-Butyl Perbenzoate

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Abstract: A simple and concise tandem cyclization of alkynoates with amines in the presence of *tert*-butyl perbenzoate (TBPB) leads to 1,2,4-trisubstituted 1*H*-pyrroles. A variety of aromatic amines and aliphatic amines can be used in this approach, and a wide range of functionalized 1,2,4-trisubstituted 1*H*-pyrroles are obtained in good to excellent yields. This protocol not only corresponds to the construction of a pyrrole fragment, but also provides a new way to form C–C and C–N bonds.

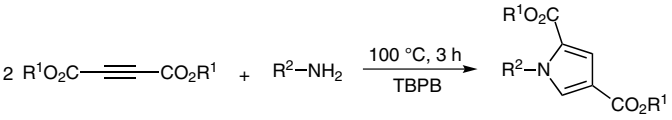
Key words: 1*H*-pyrroles, oxidation, cyclization, alkynoates, amines

In the past decades, peroxides[1] have received much attention from chemists and drug design experts, which is reflected by the plethora of publications and reviews.[2–8] This class of compounds are widely used not only in academic research as oxidant, cross-linking agent, and polymerization initiator, but also in the production of cosmetics and pharmaceuticals as active components.[9–16] *tert*-Butyl perbenzoate (TBPB) is a typical example of an organic peroxide that contains more than 8.1% active oxygen. In this paper, we describe an expeditious synthetic approach to 1,2,4-trisubstituted 1*H*-pyrroles[17,18] through TBPB-promoted tandem cyclization of alkynoates and amines (Scheme 1). It is well-known that the pyrrole fragment[19,20] is an important synthon, due to the occurrence of this unit in many molecules that are of biological and pharmaceutical interest.[21–24]

Initially, optimization of the reaction conditions was conducted; the results are summarized in Table 1. The model reaction of dimethyl but-2-ynedioate (**1a**) and *p*-toluidine (**2a**) in dioxane at 100 °C occurred in the presence of *tert*-butyl peroxide (TBHP) and resulted in formation of the product dimethyl 1-*p*-tolyl-1*H*-pyrrole-2,4-dicarboxylate (**3aa**) in 57% GC yield (entry 1). After screening reaction times, we found that three hours was optimal for completion of this reaction (entries 1–3). Among the various oxidants examined, TBPB was found to be more efficient for the explored reaction than other partners (entries 4–13). It is noteworthy that the reaction did not occur in the presence of several types of peroxides and persulfides, such as cyclohexanone peroxide, benzoyl peroxide, ammonium persulfate, oxone, and potassium persulfate (entries 4–7 and 9). Results of the screening study of the amount of TBPB indicated that 2.3 equivalent of TBPB was sufficient for the reaction (entries 14–16). Finally, we investigated the effect of solvent for this protocol and found that dioxane was most suitable (entries 15 and 17–20).

We then conducted a survey of the substrate scope of this protocol. The results, compiled in Table 2, demonstrate that a range of reactions could be performed with various alkynoates **1** and amines **2**. It was observed that all the reactions were quite sensitive to the electronic contribution of the substituents on the benzene ring of the aromatic amines; amines such as **2a**–**g**, with electron-donating groups on the benzene ring, all afforded the corresponding 1,2,4-trisubstituted 1*H*-pyrrole **3aa**–**ag** in good to excellent isolated yields, whereas substrates with electron-withdrawing groups on the benzene ring, such as 4-nitrobenzenamine and 2,4-dinitrobenzenamine, did not react, presumably due to the strong electron-withdrawing effect of the nitro group on the benzene ring. All the tested aliphatic amines reacted smoothly and afforded the corresponding product **3ah** and **3ai** in excellent isolated yield. Additionally, diethyl but-2-ynedioate (**1b**) also reacted with *p*-toluidine (**2a**) to smoothly give the corresponding pyrrole **3ba** in good isolated yield. This result demonstrated that diethyl but-2-ynedioate was a good partner of dimethyl but-2-ynedioate for this protocol. However, when other types of electron-deficient alkynoates, such as ethyl 3-phenylpropiolate, ethyl but-2-ynoate, and methyl oct-2-ynoate, were used as partners of dimethyl but-2-ynedioate in this protocol, none of the desired product was observed.

To probe the mechanism of this transformation, two control experiments were performed. Dimethyl 2-(*p*-tolyl-



Scheme 1 Synthesis of 1,2,4-trisubstituted 1*H*-pyrroles

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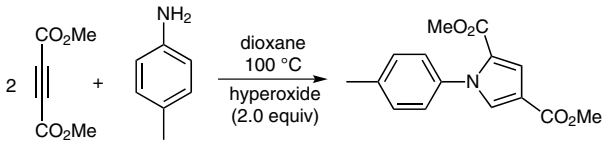
Table 1 Optimization of Reaction Conditions[a]



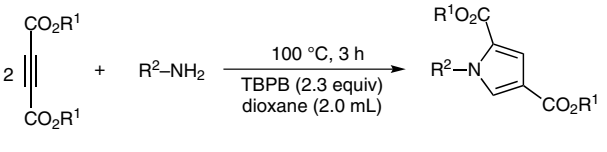
1a **2a** **3aa**

Entry	Solvent	Time (h)	Peroxide (2.0 equiv)	Yield (%)[b]
1	dioxane	2	TBHP	57
2	dioxane	3	TBHP	65
3	dioxane	4	TBHP	65
4	dioxane	3	ammonium persulfate	none
5	dioxane	3	benzoyl peroxide	none
6	dioxane	3	oxone	none
7	dioxane	3	potassium persulfate	none
8	dioxane	3	dicumyl peroxide	51
9	dioxane	3	cyclohexanone peroxide	none
10	dioxane	3	TBHP	32
11	dioxane	3	TBPB	88
12	dioxane	3	cumene hydroperoxide	47
13	dioxane	3	methyl ethyl ketone peroxide	26
14	dioxane	3	TBPB (1.0 equiv)	63
15	dioxane	3	TBPB (2.3 equiv)	92
16	dioxane	3	TBPB (3.0 equiv)	92
17	DMF	3	TBPB (2.3 equiv)	63
18	DMSO	3	TBPB (2.3 equiv)	47
19	DCE (80 °C)	3	TBPB (2.3 equiv)	33

[a] Reaction conditions: **1a** (0.50 mmol), **2a** (0.25 mmol), solvent (2.0 mL).
[b] GC yield.

amino)but-2-enedioate and tetramethyl 1-*p*-tolyl-1*H*-pyrrole-2,3,4,5-tetracarboxylate were employed as reactants under the same conditions (Scheme 2). Interestingly,

Table 2 Substrate Scope with Isolated Yields

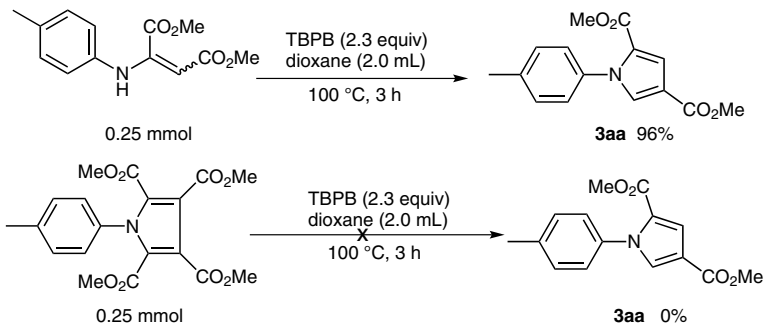


1 **2** **3**

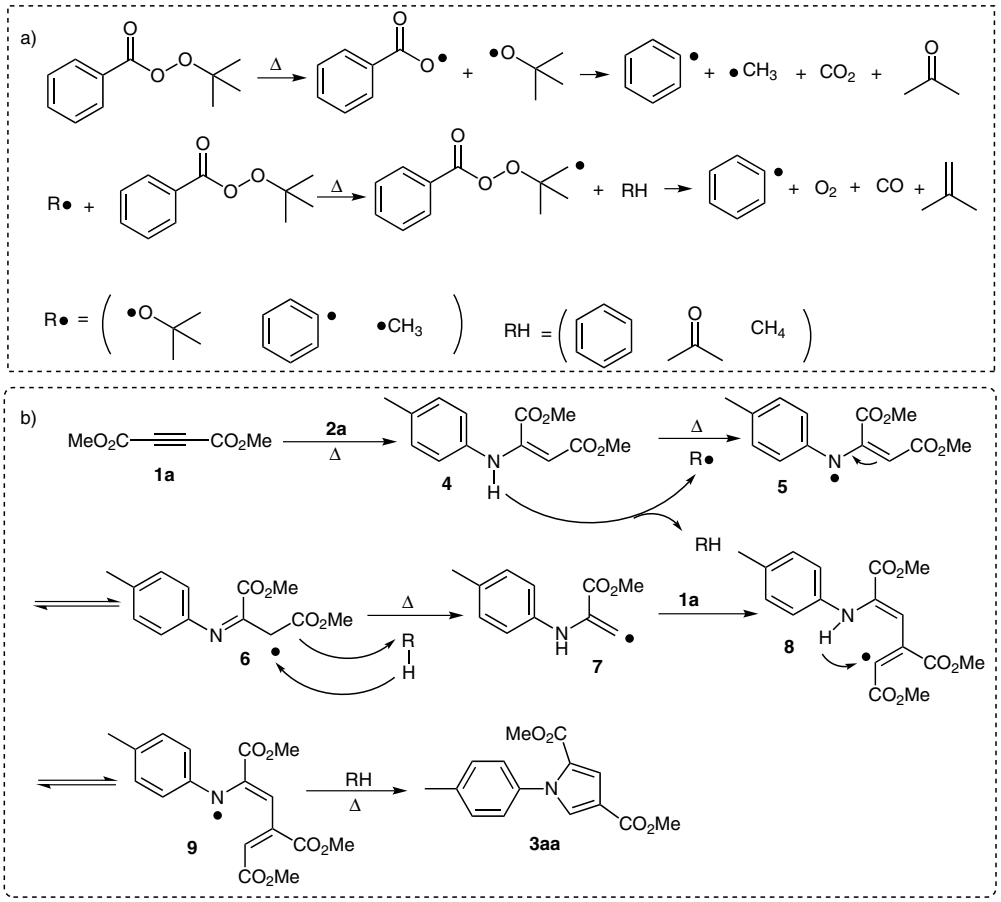
1	R^1	**2**	R^2	**3**	Yield (%)
1a	Me	**2a**	4-MeC_6H_4	**3aa**	89
1a	Me	**2b**	4-$MeOC_6H_4$	**3ab**	94
1a	Me	**2c**	3-MeC_6H_4	**3ac**	83
1a	Me	**2d**	4-ClC_6H_4	**3ad**	78
1a	Me	**2e**	Ph	**3ae**	82
1a	Me	**2f**	4-BrC_6H_4	**3af**	86
1a	Me	**2g**	1-naphthyl	**3ag**	81
1a	Me	**2h**	Bn	**3ah**	85
1a	Me	**2i**	Bu	**3ai**	85
1b	Et	**2j**	4-MeC_6H_4	**3ba**	79

we were pleased to find that the reaction proceeded smoothly and gave product **3aa** in almost quantitative yield when using 2-(*p*-tolylamino)but-2-enedioate as the substrate. However, no desired product **3aa** was detected when 1-*p*-tolyl-1*H*-pyrrole-2,3,4,5-tetracarboxylate was used as the substrate.

On the basis of these preliminary results, a plausible mechanism of this peroxidation was hypothesized as shown in Scheme 3, exemplified by the formation of **3aa**. The first step involves peroxide decomposition;[25,26] TBPB generates two oxy radicals during the thermal homolytic cleavage process. During the course of the reaction, large numbers of gas bubbles were evolved that were confirmed as carbon dioxide by a lime water test; this phenomenon indicated that the oxy radicals continuously reacted with TBPB or decomposed to produce other radicals (Scheme 3, a).[27,28] The following step involves the formation of hydroamination product **4** (Scheme 3, b). The resulting peroxyl radical from TBHP can react with aminyl to form the unstable aminyl radical **5**. Through 1,3-hydrogen radical



Scheme 2 Control experiments



Scheme 3 Hypothesized mechanism

transfer, **5** can easily rearrange to allylic radical **6**, which reacts with RH to generate a new carbon radical **7** by elimination of one equivalent of RCO_2Me under the high temperature conditions. Radical attack of **7** on the C–C triple bond of alkynoate **1a** then affords another radical, **8**, which quickly converts into the new aminyl radical **9** through 1,5-hydrogen radical transfer. Subsequent radical attack of **9** on the olefinic carbon affords the final product **3aa** accompanied by elimination of RCO_2Me.

In summary, we have discovered a practical, general method involving peroxidation to directly construct a 1,2,4-trisubstituted pyrrole framework.[29] The approach requires short reaction times, uses an inexpensive organic peroxide as the oxidant, and provides the product selectively in good to excellent yield. Furthermore, although a large body of literature exists on thermally induced peroxidation by peroxides, this protocol, which involves oxidative cleavage of a C–C bond mediated by TBPB, has not been documented. Further investigations focusing on clarifying the mechanism and extending the application of this reaction are underway in our group, and the results will be reported in the near future.

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

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(29) **Synthesis of Dimethyl 1-*p*-Tolyl-1*H*-pyrrole-2,4-dicarboxylate (3aa); Typical Procedure:** A mixture of **1a** (284 mg, 2.0 mmol), *p*-toluidine (107 mg, 1.0 mmol), TBPB (446 mg, 2.3 mmol) and dioxane (2.0 mL) was added successively to a Schlenk tube. After stirring for 3 h at 100 °C, the solution was directly subjected to isolation by PTLC (GF_{254}; PE–EtOAc, 10:2) to afford the desired product **3aa** (243 mg, 89%). Yellow oil; IR (KBr): 2951, 2857, 1717, 1640, 1516, 1475, 1443, 1257, 1160, 1044, 978, 912, 167, 740 cm^{-1}; ^1H NMR ($CDCl_3$, 400 Hz): δ = 7.21–7.14 (q, *J* = 8.4 Hz, 4 H), 6.77–6.76 (d, *J* = 3.2 Hz, 1 H), 6.22–6.22 (d, *J* = 3.2 Hz, 1 H), 3.81 (s, 3 H), 3.71 (s, 3 H), 2.37 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 Hz): δ = 164.4, 162.1, 138.3, 136.7, 129.7, 127.0, 125.0, 124.9, 119.1, 110.8, 52.3, 51.6, 21.0; MS (EI): *m*/*z* (%) = 242.05 (100.00), 273.05 (86.88); Anal. Calcd for $C_{15}H_{15}NO_4$: C, 65.92; H, 5.53; N, 5.13. Found: C, 66.07; H, 5.45; N, 5.30.

