A solvent-free synthesis of ethyl 3,5-diaryl-1*H*-pyrrole-2-carboxylates via triethylphosphite mediated reductive cyclization of ethyl 2-nitro-5-oxo-3,5-diarylpentanoates under microwave irradiation

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A solvent-free synthesis of ethyl 3,5-diaryl-1*H*-pyrrole-2-carboxylates via triethylphosphite mediated reductive cyclization of ethyl 2-nitro-5-oxo-3,5-diarylpentanoates under microwave irradiation

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Abstract

Ethyl 3,5-diaryl-1*H*-pyrrole-2-carboxylates have been synthesized in good yields from ethyl 2-nitro-5-oxo-3,5-diarylpentanoates by treatment with triethylphosphite under microwave irradiation. The integrity of the mechanism proposed has been augmented by ^{31}P NMR and EIMS experiments.

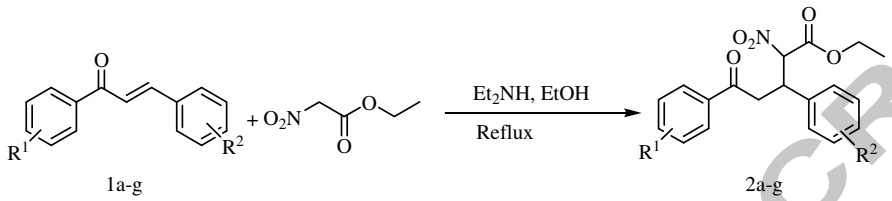
Keywords:reductive cyclization, ethyl 2-nitro-5-oxo-3,5-diarylpentanoates, triethylphosphite, ethyl 3,5-diaryl-1*H*-pyrrole-2-carboxylates, microwave irradiation.

Pyrroles are an important class of nitrogen-containing heterocycles[1] found widely in natural and bio-active molecules,[2] possessing antibacterial,[3] antifungal,[4] antiinflammatory,[5]antioxidative,[6] antitumor,[7] antitubercular,[8]hypolipidemic[9] and immune suppressant activities.[10] In addition, they act as inhibitors of retroviral reverse transcriptases [*i.e*., human immunodeficiency virus type 1 (HIV 1)], cellular DNA polymerasesand protein kinases.[11] There are several pyrrole moiety containing drugs available in the market and some of them are: atrovastatin (Lipitor)(*hyperlipidemic*),[12] BM 212 (*antifungal and antimycobacterial*),[13] tallimustine (*anticancer*), pyrrolomycin B, pyoluteorin and pyrrolnitrin (*antibiotics*).[14] The most celebrated biological context of pyrroles is the tetrapyrrole scaffold of heme and related porphinoid co-factors *e.g.* heme b, vitamin B_{12}, chlorophyll α and factor 430. Furthermore, pyrroles are important structural motifs of natural alkaloids, co-enzymes[15] and unnatural heterocyclic derivatives. They are also widely used in materials science[16] as semi conductors, chemosensors, fluorescent sensors and for image diagnosis.

There are many methods for the synthesis of pyrrole derivatives, including the classical Hantzch procedure,[17] cyclocondensation of α-aminoketones with β-ketoesters or β-diketones (Knorr synthesis),[18] cyclocondensation of primary amines with 1,4-dicarbonyl compounds (Paal Knorr synthesis),[19] 1,3-dipolar cycloaddition of azomethine ylides to alkynes followed by aromatization of the intermediate pyrrolines,[20] Cu-assisted cycloisomerization of alkynyl imines,[21] rhodium-catalysed hydroformylation of β-alkynylamines with CO/H_2,[22] condensation of nitroolefins or esters of vicinal nitro alcohols with stabilized α-isocyano anions,[23] rhodium(II) acetate-catalysed intramolecular N-H insertion reaction of δ-amino-γ,γ-difluoro-α-diazo-β-ketoesters,[24] reductive cyclization of 2-aryl succinonitriles[25] and various other cycloaddition and transition metal-catalysed cyclization strategies.[26] Ethyl 3,5-diaryl-1*H*-pyrrole-2-carboxylates have been prepared from ethyl 2-nitro-5-oxo-3,5-diarylpentanoates by heating with reducing systems such as a combination of tributylphosphine and diphenyldisulphide,[27] formamidinesulfinic acid (thiourea-S,S-dioxide).[28] However, most of these methods suffer from one or more disadvantages such as the involvement of multistep laborious protocols, use of harsh reaction conditions, use of expensive reagents, tedious work-up procedures and generation of toxic by-products. Triethyl phosphite has been used in the syntheses of carbazoles, indoles, indazoles and related compounds.[29] In our continuing efforts[30] to develop newer methodologies in organic synthesis, we contemplated the use of

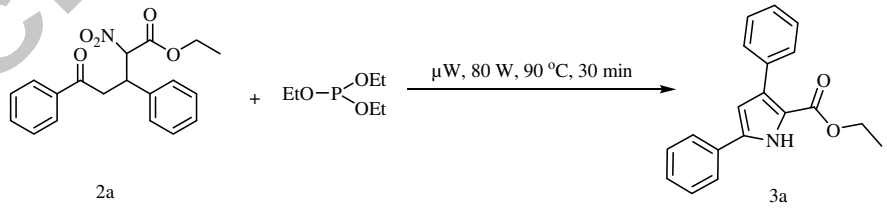
triethylphosphite for the synthesis of ethyl 3,5-diaryl-1*H*-pyrrole-2-carboxylates via reductive cyclization of ethyl 2-nitro-5-oxo-3,5-diarylpentanoates.

Firstly the requisite starting materials *viz.* ethyl 2-nitro-5-oxo-3,5-diarylpentanoates (γ-nitroketones) **2a-g** were synthesized by the reaction of 1,3-diarylpropenones (chalcones) **1a-g** with ethylnitroacetate following the Davey and Tivey procedure[31] using diethylamine as a base in ethanol (Scheme1). 1,3-Diarylpropenones were, in turn, prepared by an aldol/dehydration reaction of the corresponding aldehyde and acetophenone.[32]



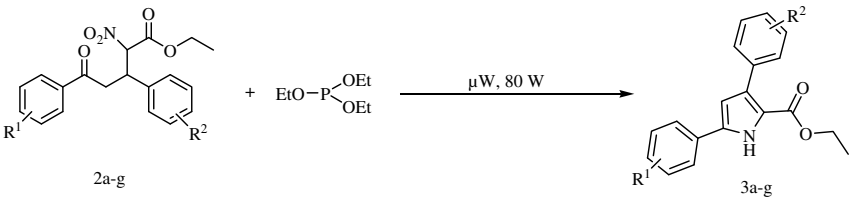
Scheme 1. Synthesis of ethyl 2-nitro-5-oxo-3,5-diarylpentanoates **2a-g**.

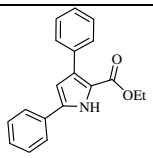
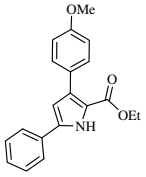
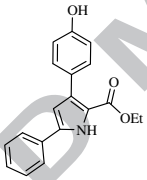
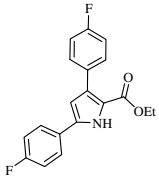
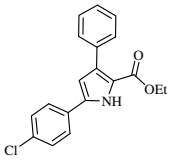
The above prepared ethyl 2-nitro-5-oxo-3,5-diphenylpentanoate **2a**(1.0 mmol) was taken in triethylphosphite (3.0 mmol) without any solvent and was exposed to microwave irradiation [power 80 W, 90 ^{o}C] for 30 min (TLC). To our delight, the formation of the expected product ethyl 3,5-diphenyl-1*H*-pyrrole-2-carboxylate **3a**, as characterized by comparison of its physical and spectral data[33] with the authentic sample,[34] was noticed (Scheme 2).The above mentioned reaction upon conventional heating at 120 ^{o}C for 3 h also resulted in the formation of desired product **3a** but the yield of the product (18%) was very low and starting material was recovered intact. Moreover, microwave heating has been extensively used for carrying out chemical reactions and has become a useful non-conventional energy source for speeding-up organic syntheses.[35] Replacing triethylphosphite with trimethylphosphite without changing the reaction conditions [$P(OMe)_3$: 3 equivalents, MWI, 90 ^{o}C, 30 min] was found to be equally successful and the desired product **3a** was obtained in 89% yield. It was observed that trimethylphosphite was a strong irritant with severe pungent smell and was found extremely difficult to handle. In view of these facts, we decided to pursue future experiments with triethylphosphite under microwave irradiation. To explore the scope of this methodology, a variety of ethyl 2-nitro-5-oxo-3,5-diarylpentanoates **2a-g** were subjected to aforementioned reductive cyclization reaction and the formation of the desired products **3a-g** was observed in good to excellent yields (82-94%, Table 1).

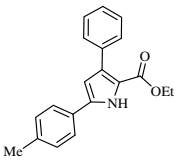
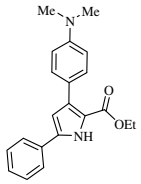


Scheme 2. Synthesis of ethyl 3,5-diphenyl-1*H*-pyrrole-2-carboxylate **3a**.

Table 1: Triethylphosphite mediated synthesis of ethyl 3,5-diaryl-1*H*-pyrrole-2-carboxylates **3a-g**



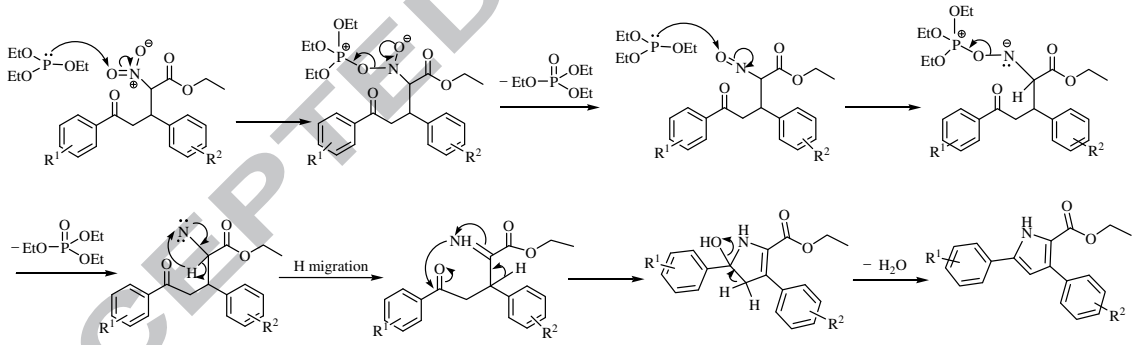
Entry	R^1	R^2	Product[a]	Mp[b] [lit. mp °C]	Time (min)	Yield[c] (%)
1	H	H	 **3a**	136-138 [139-140][34]	30	90
2	H	4-OMe	 **3b**	131-133 [135][36]	50	87
3	H	4-OH	 **3c**	207-209 [205-206][37]	40	82
4	4-F	4-F	 **3d**	147-149 [149-150][37]	50	93
5	4-Cl	H	 **3e**	182-183 [185][36]	50	94

6	4-Me	H	 **3f**	167-169 [168-170][38]	45	89
7	H	4-N(Me)$_2$	 **3g**	137-138 [135-137][34]	40	83

[a]All the products were identified by comparison of their physical and spectral data with those of authentic samples.
[b]Literature reference of melting point.
[c]Isolated yield.

It is pertinent to mention that this methodology is not limited only to diaryl substituents since a reaction of ethyl 2-nitro-5-oxo-3-methyl-5-phenylpentanoate under similar conditions [P(OEt)$_3$: 3 equivalents, MWI, 90 ^{o}C, 30 min] yielded ethyl 3-methyl-5-phenyl-1*H*-pyrrole-2-carboxylate[39] in 82% yield.

In light of the mechanism proposed by Cadogen *et al*.,[29] and Hollima*net al*.,[40] following mechanism is proposed for the current reaction.



Scheme 3. Mechanism for the P(OEt)$_3$ promoted reductive cyclization of ethyl 2-nitro-5-oxo-3,5-diarylpentanoates **2a-g**.

To establish the integrity of the above proposed mechanism leading to the formation of triethylphosphate in the reaction, ^{31}P NMR ($CDCl_3$, 162 MHz) and EIMS experiments were conducted. It was found that the singlet at δ:138.7 ppm, corresponding to phosphorus in triethylphosphite disappeared from the spectrum of the aliquot taken from the reaction mixture [**2a**, P(OEt)$_3$, MWI] after 30 min, revealing the disappearance of triethyl phosphite with the appearance of a singlet at δ: -0.87 ppm corresponding to triethylphosphate. Also the presence of two singlets at δ 9.47 and 5.20 ppmin the ^{31}P NMR suggests the formation of diethyl phosphite in the reaction by the hydrolysis of triethylphosphite. EIMS of this aliquot displayed diagnostic molecular ion peaks at *m/z* 183

$(M+H)^+$ and 205 $(M+Na)^+$ corresponding to triethylphosphate and at *m/z* 139 $(M+H)^+$ and 161 $(M+Na)^+$ corresponding to diethylphosphite.

In summary, an efficient method for the preparation of ethyl 3,5-diaryl-1*H*-pyrrole-2-carboxylates has been developed via reductive cyclization of various ethyl 2-nitro-5-oxo-3,5-diphenylpentanoates with triethylphosphite under microwave irradiation without any solvent.

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33. *Procedure for the synthesis of ethyl 3,5-diphenyl-1H-pyrrole-2-carboxylate* ***3a***: A mixture of ethyl 2-nitro-5- oxo-3,5-diphenylpentanoate (0.341 g, 1.0 mmol) and triethylphosphite (0.498 g, 3.0 mmol) in a closed vessel was irradiated in a microwave synthesizer (CEM Discover) at 90 ^{o}C(80 W) for 30 min. After completion of the reaction (TLC), the reaction mixture was cooled to room temperature and the volatiles were removed under vacuum at 70 ^{o}C to give a brown colored residue, which was taken in ethyl acetate (30 mL). The ethyl acetate solution was washed with water (3 × 15 mL), brine (1 × 15 mL), dried (anhydrous Na_2SO_4) and concentrated on rotary evaporator. The resultant after column chromatography over silica (60-120mesh) using a gradient of a mixture of petroleum ether-ethyl acetate yielded crystalline ethyl 3,5-diphenyl-1*H*-pyrrole-2-carboxylate **3a** (0.262 g, 90%). Mp. 136-138^{o}C (lit. m.p. 139-140^{o}C).[34] ^{1}H NMR ($CDCl_3$, 400MHz): δ (ppm) 9.45 (br s, 1H, exchangeable with D_2O), 7.64-7.61(m, 4H), 7.50-7.30 (m, 6H), 6.66 (d,J = 3.2 Hz, 1H), 4.31 (q, J = 7.2 Hz, 2H), 1.28 (t, J = 7.2 Hz,3H); ^{13}CNMR ($CDCl_3$, 100 MHz): δ (ppm) 161.27, 135.38, 135.08, 133.46, 131.06, 129.56, 129.09, 128.36, 127.95, 127.69, 127.14, 124.78, 118.60, 109.95, 60.45, 14.25; IR (KBr) ($\upsilon_{max,}$ cm^{-1}): 3313, 1662; Anal. Calcd for $C_{19}H_{17}NO_2$: C, 78.33; H, 5.88; N, 4.81%. Found: C, 78.38; H, 5.82; N, 4.73%. MS(ESI) (*m/z*): 292 $(M+H)^+$.
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Graphical abstract

A solvent-free synthesis of ethyl 3,5-diaryl-1*H*-pyrrole-2-carboxylates via triethylphosphite mediated reductive cyclization of ethyl 2-nitro-5-oxo-3,5-diarylpentanoates under microwave irradiation

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