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Synthesis of 4-(1,3-dioxo-2,3-dihydro-1*H*-2-indenyl) substituted 1-benzylpyrrole-3-carboxylates *via* a tandem four-component reaction

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ABSTRACT

An efficient approach for the preparation of functionalized 4-(1,3-dioxo-2,3-dihydro-1*H*-2-indenyl) substituted 1-benzylpyrrole-3-carboxylates is described. This four-component reaction between ninhydrin, 1-phenyl-2-(1,1,1-triphenyl-λ^5-phosphanylidene)-1-ethanone, primary amines and alkyl acetoacetate proceeds in MeOH under reflux condition in good to excellent yields.

1. Introduction

Multicomponent reactions (MCRs) are excellent strategies, being employed in the synthesis of many natural products. These MCRs are generally defined as reactions where more than two starting materials react to form a product, incorporating more or less all the atoms of the starting materials [1]. The MCRs offer a wide range of advantages such as a single-step procedure, avoiding complicated purification processes and saving both solvents and reagents.

The MCRs have attracted considerable interest owing to their exceptional synthetic efficiency. Recently, there has been tremendous development in three- and four-component reactions [2].

Five-membered, *N*-containing heterocycles are important building blocks of an extensive number of biologically active compounds [3]. Among them, pyrroles are heterocycles of great importance because of their presence in numerous natural products like heme, chlorophyll, vitamin B12, and various cytochrome enzymes [4]. Some of the recently isolated pyrrole containing marine natural products has been found to exhibit considerable cytotoxicity and to function as multidrug-resistant reversal agents [5]. Many of these biologically active compounds have emerged as chemotherapeutic agents. In addition, polysubstituted pyrroles are molecular frameworks with immense importance in material science [6].

Consequently, a wide range of procedures have been devised for the synthesis of pyrroles [7]. However, many of the methods are associated with various drawbacks such as harsh reaction conditions, tedious experimental procedures, unsatisfactory yields, and long reaction times. Moreover, the number of methods for the synthesis of polysubstituted pyrroles is relatively limited. Herein we report an efficient, new approach for the synthesis of polysubstituted pyrroles.

As part of our program aimed at developing new reactions for the preparation of heterocyclic compounds [8], very recently, we have reported the synthesis of novel spiro[indoline-3,4′-pyridine]-3′-carboxylates **1** and spiro[indole-3,6′-[1,3]thiazin]-2-ones **2** (Fig. 1) by using of 1-phenyl-2-(1,1,1-triphenyl-λ^5-phosphanylidene)-1-ethanone as a new important reagent in heterocyclic synthesis based on a one-pot reaction [9].

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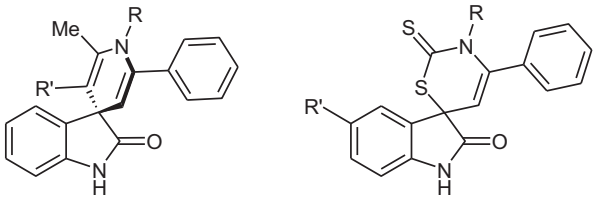


Fig. 1. A new class of important spiroheterocyclic compounds.

Also, in continuation of our works on this reagent, we have observed that the reaction between ninhydrin, 1-phenyl-2-(1,1,1-triphenyl-λ^5-phosphanylidene)-1-ethanone, and alkyl acetoacetae in presence of different amines in MeOH produced the corresponding substituted pyrroles at reflux condition (Scheme 1).

2. Results and discussion

The choice of an appropriate reaction medium is of crucial importance for successful synthesis. Initially, the four-component reaction of ninhydrin and 1-phenyl-2-(1,1,1-triphenyl-λ^5-phosphanylidene)-1-ethanone in the presence of benzylamine and methyl acetoacetate as a simple model substrate was investigated to establish the feasibility of the strategy and to optimize the reaction conditions.

Different solvents such as methanol, ethanol, acetonitrile, tetrahydrofuran (THF) and dichloromethane were explored. The results are summarized in Table 1.

As can be seen in Table 1, the best result was obtained by refluxing the reaction mixture in methanol to yield product **5a** in good yield (Table 1, Entry 1). Encouraged by this success, we extended this reaction of ninhydrin with 1-phenyl-2-(1,1,1-triphenyl-λ^5-phosphanylidene)-1-ethanone, alkyl acetoacetate **3** and a range of aromatic and aliphatic amines **4** with both electron withdrawing and electron releasing substituents under similar conditions (MeOH), and corresponding pyrroles **5** were synthesized in high yields (81–87%) and the results are summarized in Table 2. We have shown that the use of a wide diversity of substituents in amines **4** and alkyl acetoacetate **3** in this four-component reaction makes possible the synthesis of libraries under similar circumstances (Table 2).

Table 1
Synthetic results of **5** under different reactions conditions.

Entry	Solvent	Temp	Time/h	Yield (%)[a]
1	Methanol	Reflux	12	87
2	Ethanol	Reflux	8	73
3	Acetonitrile	Reflux	8	61
4	THF	Reflux	10	65
5	Dichloromethane	Reflux	10	25

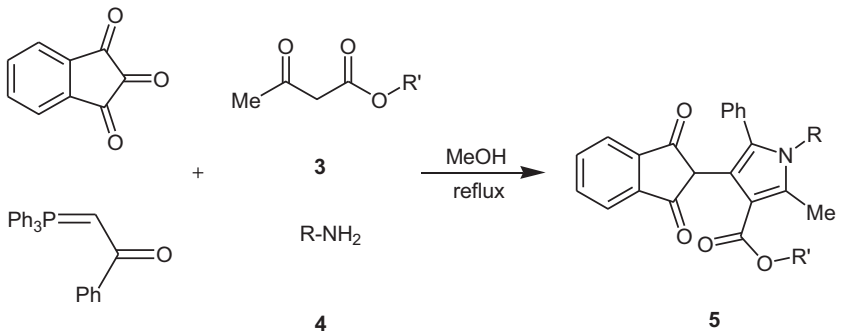
[a] Isolated yield

Table 2
Synthesis of polysubstituted pyrroles.

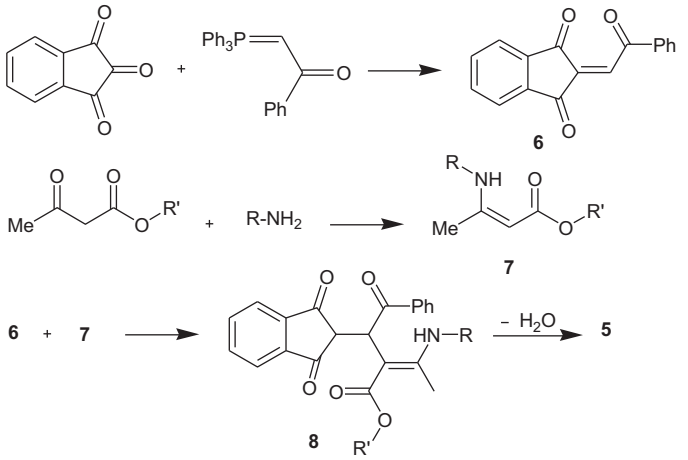
Product	R	R'	Time	Yield (%)
5a	$C_6H_5CH_2$-	Me	6	87
5b	$C_6H_5CH_2$-	Et	8	83
5c	4-$ClC_6H_4CH_2$-	Me	6	84
5d	4-$ClC_6H_4CH_2$-	Et	7	86
5e	4-$MeC_6H_4CH_2$-	Me	8	81
5f	C_6H_5-	Me	8	86
5g	n-Butyl	Me	10	82

The structures of compounds **5a–g** were deduced from their elemental analysis, IR and high-field ^1H and ^{13}C NMR spectra. The mass spectrum of **5a** displayed the molecular ion peak at $m/z = 449$, which is in agreement with the proposed structure. The IR spectrum of this compound showed absorption bands due to the CH at 2947 and the C = O group at 1694 cm^{-1}. The ^1H NMR spectrum of **5a** showed four singlet signals for the CH_3, OCH_3, CH, and CH_2 groups at $\delta = 2.44$, 3.05, 4.16 and 5.05 ppm respectively, and the aromatic moieties gave rise to multiplets in the aromatic region of the spectrum ($\delta = 6.93$–8.01 ppm). The ^1H-decoupled ^{13}C NMR spectrum of **5a** showed 21 distinct resonances in agreement with the suggested structure.

Although we have not established the mechanism of reaction experimentally, a possible explanation is proposed in Scheme 2. Compound **5** could result from the initial addition of the amine to alkyl acetoacetate and subsequent attack of the resulting reactive enaminone **7** on the compound **6** to yield intermediate **8**. Cyclization of the intermediate **8** and subsequent loss of H_2O lead to compound **5**.



Scheme 1. Synthesis of polysubstituted pyrroles.



Scheme 2. Probing the mechanism for the formation of title compounds.

3. Conclusions

In summary, a simple and easy approach has been developed for the quick construction of alkyl benzyl-4-(2,3-dihydro-1,3-dioxo-1*H*-2-indenyl)-1*H*-pyrrole-3-carboxylates **5** by the reaction of amines, alkyl acetoacetate, ninhydrin and 1-phenyl-2-(1,1,1-triphenyl-λ^5-phosphanylidene)-1-ethanone. These types of heterocycles contain a number of functional groups and are therefore valuable precursors for diversity-oriented synthesis of pyrroles libraries, which are of potential uses in the facile preparation of biologically active molecules.

4. Experimental

4.1. Materials and techniques

All reactions were carried out in oven-dried glassware. Progress of reactions was monitored by thin layer chromatography while purification was effected by column chromatography, using silica gel (Merck 230-240 mesh). Melting points were measured on an Electrothermal 9100 apparatus. Elemental analyses for C, H and N were performed using a Heraeus CHN–O–Rapid analyzer. Mass spectra were recorded on a FINNIGAN-MATT 8430 mass spectrometer operating at an ionization potential of 70 eV. ^{1}H and ^{13}C NMR spectra were measured ($CDCl_3$) with a Bruker DRX-500 AVANCE spectrometer at 500.1 and 125.8 MHz, respectively. IR spectra were recorded on a Shimadzu IR-460 spectrometer; absorbencies are reported in cm^{-1}.

4.2. General procedure for the preparation of compounds 5a–g, exemplified on 5a

A solution of 1-phenyl-2-(1,1,1-triphenyl-λ^5-phosphanylidene)-1-ethanone (0.38 g, 1 mmol), ninhydrin (0.16 g, 1 mmol) was magnetically stirred in 5 mL of MeOH for 20 min. Then, benzylamine (0.11 g, 1 mmol) and methyl acetoacetate (1.2 mmol) were added simultaneously. The reaction mixture was stirred for 6 h under reflux conditions and the progress of the reaction was followed by thin layer chromatography. When the reaction mixture was cooled to room temperature, a white solid precipitated. The precipitates were filtered and washed with diethyl ether to give product **5a** in 87% yields. All products gave satisfactory spectral data in accordance with the assigned structures.

4.3. Spectral data

Methyl 1-benzyl-4-(1,3-dioxo-2,3-dihydro-1H-2-indenyl)-2-methyl-5-phenyl-1H-3-pyrrolecarboxylate (5a): White crystals (yield 87%); mp: 214-216 °C; IR (KBr) (ν_{max}, cm^{-1}): 2947 (CH), 1694 (C = O), 1447 (Ar). ^{1}H NMR (500.13 MHz, $CDCl_3$): δ_H (ppm) 2.44 (3H, s, CH_3), 3.05 (3H, s, OCH_3), 4.16 (1H, s, CH), 5.05 (2H, s, CH_2), 6.93 (2H, d, $^3J_{HH}$ = 7.2 Hz, 2 CH of Ar), 7.25 (1H, t, $^3J_{HH}$ = 6.8 Hz, CH of Ar), 7.31 (5H, m, 5 CH of Ar), 7.40 (2H, m, 2 CH of Ar), 7.81-7.83 (2H, m, 2 CH of Ar), 8.00- 8.01 (2H, m, 2 CH of Ar). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ_C (ppm) 11.85, 48.02, 49.50, 54.95, 109.30, 112.78, 122.90, 125.68, 127.31, 128.56, 128.61, 128.82, 130.30, 131.19, 134.77, 137.08, 137.19, 137.48, 141.73, 164.63, 199.00. MS (EI, 70 eV): *m/z* (%) = 449 (M^+, 12), 417 (38), 326 (20), 73 (100). Anal. calcd for $C_{29}H_{23}NO_4$ (449.50): C, 77.49; H, 5.16; N, 3.12%. Found: C, 77.42; H, 5.10; N, 3.06%.

Ethyl 1-benzyl-4-(1,3-dioxo-2,3-dihydro-1H-2-indenyl)-2-methyl-5-phenyl-1H-3-pyrrolecarboxylate (5b): White crystals (yield 83%); mp: 205-207 °C; IR (KBr) (ν_{max}, cm^{-1}): 2926 (CH), 1683 (C = O), 1448 (Ar). ^{1}H NMR (500.13 MHz, $CDCl_3$): δ_H (ppm) 0.84 (3H, t, $^3J_{HH}$ = 5.8 Hz, CH_3), 2.44 (3H, s, CH_3), 3.65 (2H, q, $^3J_{HH}$ = 5.8 Hz, CH_2), 4.17 (1H, s, CH), 5.05 (2H, s, CH_2), 6.94 (2H, d, $^3J_{HH}$ = 6.4 Hz, 2 CH of Ar), 7.25 (1H, m, CH of Ar), 7.32 (5H, m, 5 CH of Ar), 7.39 (2H, m, 2 CH of Ar), 7.81 (2H, m, 2 CH of Ar), 7.99 (2H, m, 2 CH of Ar). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ_C (ppm) 11.52, 13.54, 47.53, 54.75, 58.46, 109.23, 112.17, 122.39, 125.22, 126.80, 128.06, 128.08, 128.32, 129.87, 130.69, 134.27, 136.53, 136.70, 136.75, 141.29, 163.94, 198.44. MS (EI, 70 eV): *m/z* (%) = 463 (M^+, 46), 417 (68), 326 (42), 298 (38),

91(100). Anal. calcd for $C_{30}H_{25}NO_4$ (463.53): C, 77.74; H, 5.44; N, 3.02%. Found: C, 77.69; H, 5.36; N, 2.98%.

Methyl 1-(4-chlorobenzyl)-4-(1,3-dioxo-2,3-dihydro-1H-2-indenyl)-2-methyl-5-phenyl-1H-3-pyrrolecarboxylate (5c): White crystals (yield 84%); mp: 210-212 °C; IR (KBr) (ν_{max}, cm^{-1}): 2924 (CH), 1710 (2 C = O), 1684 (CO_2Me), 1453 (Ar). ^1H NMR (500.13 MHz, $CDCl_3$): δ_H (ppm) 2.43 (3H, s, CH_3), 3.05 (3H, s, OCH_3), 4.14 (1H, s, CH), 5.01 (2H, s, CH_2), 6.85 (2H, d, $^3J_{HH}$ = 8.1 Hz, 2 CH of Ar), 7.28 (2H, d, $^3J_{HH}$ = 8.2 Hz, 2 CH of Ar), 7.29-7.37 (5H, m, 5 CH of Ar), 7.82-7.83 (2H, m, 2 CH of Ar), 8.00-8.01 (2H, m, 2 CH of Ar). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ_C (ppm) 11.32, 46.90, 49.08, 54.40, 109.02, 112.48, 122.44, 126.55, 128.16, 128.25, 128.53, 129.60, 130.62, 132.72, 134.34, 135.20, 136.48, 136.75, 141.20, 164.05, 198.44. MS (EI, 70 eV): *m/z* (%) = 483 (M^+, 26), 451 (74), 326 (64), 298 (58), 125 (100). Anal. Calcd. for $C_{29}H_{22}ClNO_4$ (483.95): C, 71.97; H, 4.58; N, 2.89%. Found: C, 71.90; H, 4.54; N, 2.85%.

Ethyl 1-(4-chlorobenzyl)-4-(1,3-dioxo-2,3-dihydro-1H-2-indenyl)-2-methyl-5-phenyl-1H-3-pyrrolecarboxylate (5d): White crystals (yield 86%); mp: 256-258 °C; IR (KBr) (ν_{max}, cm^{-1}): 2960, 2922 (CH), 1713 (2 C = O), 1674 (CO_2Et), 1446 (Ar). ^1H NMR (500.13 MHz, $CDCl_3$): δ_H (ppm) 0.84 (3H, t, $^3J_{HH}$ = 5.9 Hz, CH_3), 2.43 (3H, s, CH_3), 3.65 (2H, q, $^3J_{HH}$ = 5.9 Hz, CH_2), 4.15 (1H, s, CH), 5.01 (2H, s, CH_2), 6.86 (2H, d, $^3J_{HH}$ = 7.0 Hz, 2 CH of Ar), 7.28-7.36 (7H, m, 7 CH of Ar), 7.81 (2H, m, 2 CH of Ar), 7.99 (2H, m, 2 CH of Ar). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ_C (ppm) 11.48, 13.53, 46.90, 54.69, 58.54, 109.45, 112.38, 122.42, 126.59, 128.14, 128.22, 128.52, 129.68, 130.62, 132.70, 134.32, 135.25, 136.42, 136.48, 141.26, 163.86, 198.35. MS (EI, 70 eV): *m/z* (%) = 497 (M^+, 42), 451 (82), 326 (84), 298 (72), 125 (100). Anal. Calcd. for $C_{30}H_{24}ClNO_4$ (497.97): C, 72.36; H, 4.86; N, 2.81%. Found: C, 72.30; H, 4.80; N, 2.77%.

Methyl 4-(1,3-dioxo-2,3-dihydro-1H-2-indenyl)-2-methyl-1-(4-Methylbenzyl)-5-phenyl-1H-3-pyrrolecarboxylate (5e): White crystals (yield 81%); mp: 227-230 °C; IR (KBr) (ν_{max}, cm^{-1}): 2923 (CH), 1703 (C = O), 1445 (Ar). ^1H NMR (500.13 MHz, $CDCl_3$): δ_H (ppm) 2.33 (3H, s, CH_3), 2.43 (3H, s, CH_3), 3.05 (3H, s, OCH_3), 4.17 (1H, s, CH), 5.01 (2H, s, CH_2), 6.83 (2H, d, $^3J_{HH}$ = 7.2 Hz, 2 CH of Ar), 7.12 (2H, d, $^3J_{HH}$ = 7.2 Hz, 2 CH of Ar), 7.32 (3H, m, 3 CH of Ar), 7.41 (2H, m, 2 CH of Ar), 7.82 (2H, m, 2 CH of Ar), 8.00 (2H, m, 2 CH of Ar). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ_C (ppm) 11.37, 20.51, 47.34, 48.99, 54.47, 108.71, 112.17, 122.41, 125.11, 128.05, 128.99, 129.04, 129.85, 130.68, 133.66, 134.28, 136.46, 136.58, 137.04, 141.23, 164.15, 198.56. MS (EI, 70 eV): *m/z* (%) = 463 (M^+, 58), 431 (61), 326 (52), 298 (46), 105 (100). Anal. calcd for $C_{30}H_{25}NO_4$ (463.53): C, 77.74; H, 5.44; N, 3.02%. Found: C, 77.69; H, 5.40; N, 2.98%.

Methyl 1-butyl-4-(1,3-dioxo-2,3-dihydro-1H-2-indenyl)-2-methyl-5-phenyl-1H-3-pyrrolecarboxylate (5f): White crystals (yield 86%); mp: 185-187 °C; IR (KBr) (ν_{max}, cm^{-1}): 2927 (CH), 1707 (C = O), 1533, 1439 (Ar). ^1H NMR (500.13 MHz, $CDCl_3$): δ_H (ppm) 0.78 (3H, t, $^3J_{HH}$ = 7.3 Hz, CH_3), 1.15-1.19 (2H, m, CH_2), 1.49-1.54 (2H, m, CH_2), 2.57 (3H, s, CH_3), 3.02 (3H, s, OCH_3), 3.77 (2H, t, $^3J_{HH}$ = 8.2 Hz, CH_2-N), 4.06 (1H, s, CH), 7.38-7.43 (3H, m, 3 CH of Ar), 7.48 (2H, d, $^3J_{HH}$ = 7.2 Hz, 2 CH of Ar), 7.80-7.81 (2H, m, 2 CH of Ar), 7.98-7.99 (2H, m, 2 CH of Ar). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ_C (ppm) 11.23, 12.91, 19.27, 32.07, 43.76, 48.86, 54.42, 108.03, 111.89, 122.39, 128.01, 128.05, 130.33, 130.89, 134.23, 135.77, 136.41, 141.18, 164.13, 198.68. MS (EI, 70 eV): *m/z* (%) = 415 (M^+, 82), 383 (100), 341 (42), 56 (20). Anal. Calcd. for $C_{26}H_{25}NO_4$ (415.49): C, 75.16; H, 6.06; N, 3.37%. Found: C, 75.11; H, 6.01; N, 3.30%.

Methyl 4-(1,3-dioxo-2,3-dihydro-1H-2-indenyl)-2-methyl-1,5-diphenyl-1H-3-pyrrolecarboxylate (5g): White crystals (yield 82%); mp: 217-220 °C; IR (KBr) (ν_{max}, cm^{-1}): 2924 (CH), 1707 (CO_2Me), 1526, 1441 (Ar). ^1H NMR (500.13 MHz, $CDCl_3$): δ_H (ppm) 2.37 (3H, s, CH_3), 3.10 (3H, s, OCH_3), 4.32 (1H, s, CH), 7.13-7.16 (5H, m, 5 CH of Ar), 7.22 (2H, m, 2 CH of Ar), 7.31 (3H, m, 3 CH of Ar), 7.84 (2H, m, 2 CH of Ar), 8.03 (2H, m, 2 CH of Ar). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ_C (ppm) 12.41, 49.18, 54.49, 109.01, 112.25, 122.50, 127.23, 127.58, 127.61, 128.00, 128.42, 129.91, 130.37, 134.37, 136.56, 137.01, 137.78, 141.73, 164.23, 198.58. MS (EI, 70 eV): *m/z* (%) = 435 (M^+, 34), 403 (100), 104 (24), 77 (76). Anal. Calcd. for $C_{28}H_{21}NO_4$ (435.48): C, 77.23; H, 4.86; N, 3.22%. Found: C, 77.18; H, 4.80; N, 3.17%.

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