Tetrahedron Letters 53 (2012) 2622–2626

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

One-pot four-component domino reaction for the synthesis of substituted dihydro-2-oxypyrrole catalyzed by molecular iodine

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ARTICLE INFO

Article history:
Received 14 February 2012
Revised 8 March 2012
Accepted 13 March 2012
Available online 21 March 2012

This paper is dedicated to my mentor Professor Dr. R. R. Schmidt on the occasion of his 70th birthday.

Keywords:
Multicomponent reactions
Dihydro-2-oxypyrrole derivatives
Dimethylacetylene dicarboxylate
Primary amines
Formaldehyde
Iodine

ABSTRACT

The synthesis of multi-functionalized dihydro-2-oxypyrrole can be achieved using one-pot four-component domino reaction from dialkylacetylene dicarboxylate, amines, and formaldehyde by employing molecular iodine as catalyst at room temperature. The salient features of the present method are: simple, straightforward, cost-effective, environmentally benign, and no column chromatographic separation is applicable on a broad range of substrates.

Pyrrole and its derivatives such as dihydro-2-oxypyrroles and pyrrolodines are the important structural motifs that are found in natural and unnatural products.[1] Especially, functionalized dihydro-2-oxypyrroles ring is present in a variety of alkaloids having wide biological activity and they are also used as optoelectronic materials.[2] For example, dihydro-2-oxypyrroles derivative (**1**) has been used as PI-091,[3] which is a novel platelet aggregation inhibitor and Thiomarinol A 4, a potent antibiotic as shown in Figure 1.

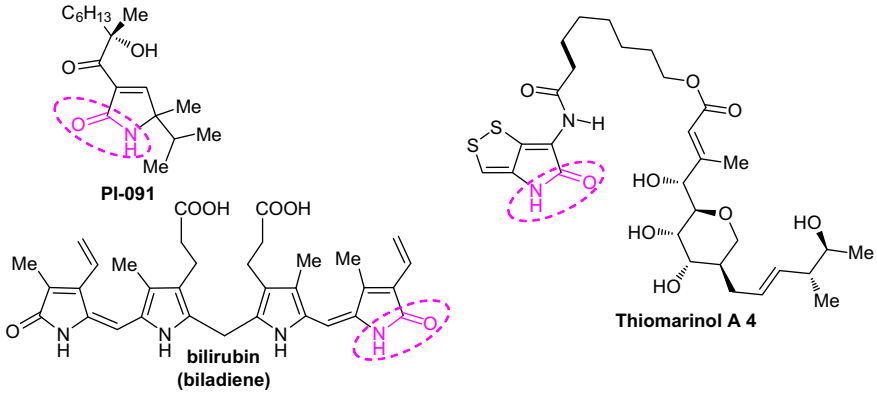

Figure 1. Biologically active compound having dihydro-2-oxypyrrole unit.

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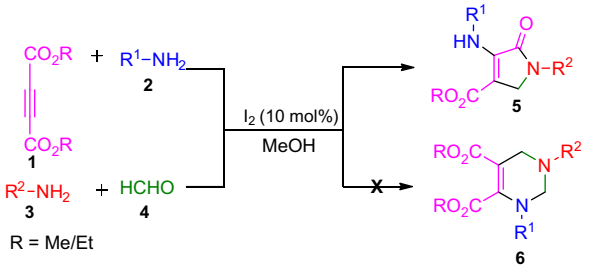
http://dx.doi.org/10.1016/j.tetlet.2012.03.046



Scheme 1. Synthesis of substituted dihydro-2-oxypyrroles.

They also act as cardiac cyclic AMP phosphodiesterase inhibitors,[4] and vascular endothelial growth factor receptors.[5] In addition, their herbicidal,[6] pesticidal,[7] and anti-tumor[8] activities as well as useful intermediates,[9] increasingly necessitate new research. Despite their wide range of applications, available routes for their synthesis are limited[10] especially, using multi-component reactions (MCRs).[11]

MCRs have emerged as a versatile approach in organic synthesis due to their advantages over the conventional multi-step synthesis.[12] In addition, they are eco-friendly, superior atom-economy,[13a] less time consuming, and costly purification processes and protection–deprotection steps can be avoided.[13b,c] Using this approach, our research group demonstrated the synthesis of various heterocycles.[14a]

According to our previous experience with molecular iodine[14b] as well as by others,[15a,b] it has been found to be a useful Lewis acid for various organic transformations due to its non-toxic, non-metallic, ready availability, and environmentally benign nature. The same catalyst has also been exploited for a diverse range of multicomponent reactions[16a–d] as well as the synthesis of various heterocycles.[16e–g] We conceived that the molecular iodine can be further utilized for the synthesis of highly substituted dihydro-2-oxypyrrole derivatives from dimethyl acetylenedicarboxylate (DMAD), amines, and formaldehyde involving MCRs. Herein, we would like to report the synthesis and mechanistic aspects of densely functionalized dihydro-2-oxypyrroles as shown in Scheme 1.

With this aim in mind, the reaction of dimethyl acetylenedicarboxylate (1 mmol), aniline (2.1 mmol), and formaldehyde (1.2 mmol) was carried out in the presence of 10 mol % of iodine in methanol at room temperature and it afforded the product **5a** in 82% yield, which was finally characterized by IR, ^{1}H NMR, ^{13}C NMR spectra and elemental analysis. Subsequently, various other catalysts were also examined for the same reaction such as $NiCl_2$, $ZnCl_2$, and BDMS (entries 5–7) to verify the efficacy of the other catalysts in terms of yield and reaction time. Likewise, different solvents were also scrutinized for example EtOH, MeCN, DCM, and THF (entries 8–11) to examine the aptness of the solvent. The results and observations are summarized in Table 1. From these observations, we may conclude that 10 mol % iodine in methanol or ethanol is found to be the most suitable reaction condition for this transformation (Table 1).

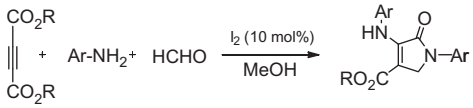
After optimization of the reaction conditions, the reaction mixture of DMAD (1 mmol), 4-methylaniline (2.1 mmol) and formaldehyde (1.2 mmol) was treated with 10 mol % iodine at rt and the desired product **5b** was obtained in 78% yield. Then, a variety of anilines with substituents Et, OMe, Cl and Br at *para* position were examined with DMAD and formaldehyde under identical conditions and the corresponding dihydro-2-oxypyrrole derivatives (**5c**–**f**) were obtained in good yields as shown in Table 1 (entries

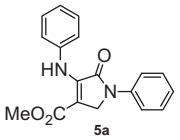
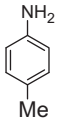
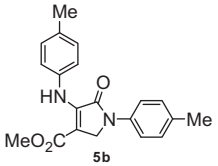
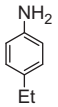
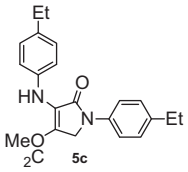
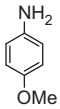
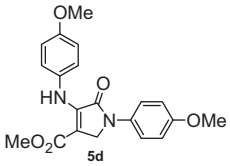
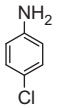
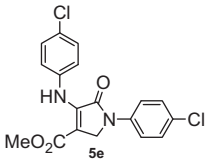
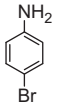
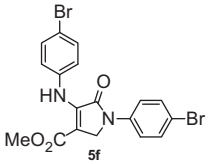
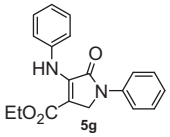
Table 1
Optimization of reaction conditions[a]

Entry	Catalyst	Catalyst (mol %)	Solvent	Time (h)	Yield[b] (%)
1	No catalyst	0	MeOH	24	Trace
2	Iodine	5	MeOH	2	60
3	Iodine	10	MeOH	1	82
4	Iodine	15	MeOH	1	80
5	$NiCl_2$	10	MeOH	8	52
6	$ZnCl_2$	10	MeOH	8	45
7	BDMS	10	MeOH	8	50
8	Iodine	10	EtOH	8	76
9	Iodine	10	MeCN	8	60
10	Iodine	10	DCM	8	42
11	Iodine	10	THF	8	40

[a] The reaction were carried out in the same scale and identical conditions.
[b] Isolated yields.

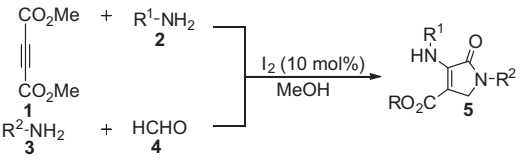
Table 2
Synthesis of various dihydro-2-oxypyrroles using anilines[17]

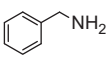
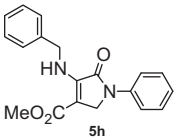
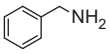
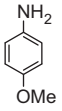
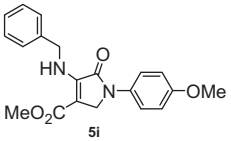
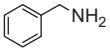
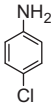
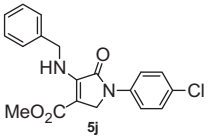
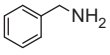
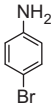
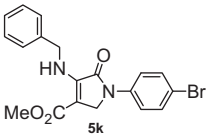
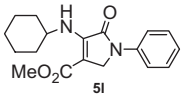
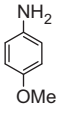
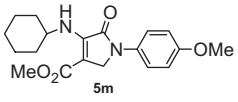
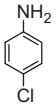
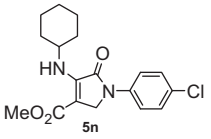
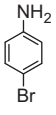
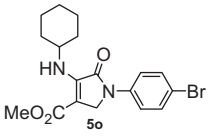
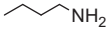
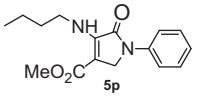
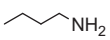
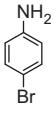
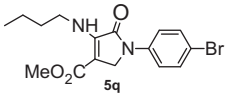
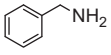
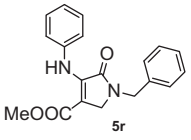


Entry	R	Ar-NH_2	Time (h)	Product[a]	Yield[b] (%)
1	Me		1.0	 **5a**	82
2	Me		1.0	 **5b**	78
3	Me		1.0	 **5c**	78
4	Me		1.5	 **5d**	76
5	Me		1.0	 **5e**	81
6	Me		1.0	 **5f**	83
7	Et		1.0	 **5g**	81

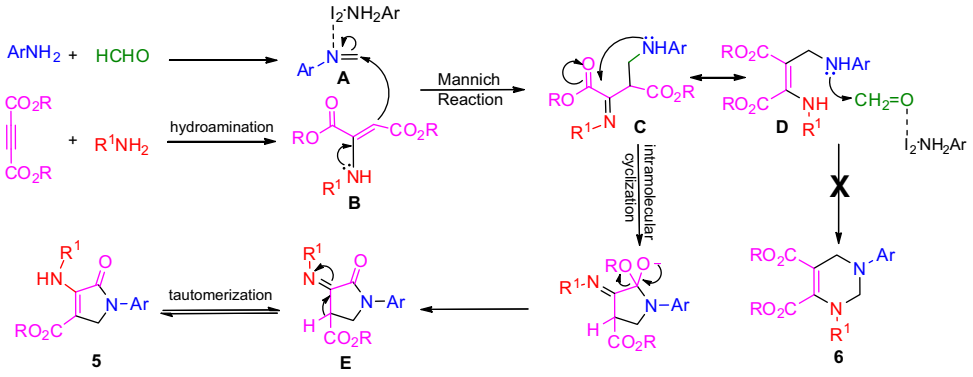
[a] All the reactions were carried out with DMAD/amine/formaldehyde (1 mmol:2.1 mmol:1.2 mmol).
[b] Isolated yields.

Table 3
Synthesis of dihydro-2-oxypyrroles using two different amines[17]



Entry	R^1NH_2	R^2NH_2	Time (h)	Product[a]	Yield[b] (%)
1			1	 5h	83
2			2	 5i	81
3			1	 5j	83
4			1	 5k	85
5			1.5	 5l	74
6			2	 5m	73
7			1.5	 5n	77
8			1.5	 5o	78
9			4	 5p	70
10			1.5	 5q	74
11			4	 5r	68

[a] All the reactions were carried out with DMAD/aliphatic amine/aromatic amine/formaldehyde (1.0 mmol:1.0 mmol:1.0 mmol:1.2 mmol).
[b] Isolated yields.



Scheme 2. Plausible mechanism for the formation dihydro-2-oxypyrroles.

3–6). To examine the effect of alkyl group in acetylenedicarboxylate, we have performed the reaction of diethyl acetylenedicarboxylate with aniline and formaldehyde in the presence of the same catalyst under identical reaction conditions and it afforded **5g** (Table 2, entry 7) in yield 81%.

Next, we explored the methods using two different amines for the synthesis of different substituted dihydro-2-oxypyrroles. The mixture of DMAD (1 mmol) and benzylamine (1 mmol) was stirred for 10–15 min at rt, and then aniline (1 mmol), formaldehyde (1.2 mmol), and 10 mol % iodine were added sequentially into the above reaction mixture. The product **5h** was isolated in 83% yield, which was characterized by IR, ^{1}H NMR, ^{13}C NMR spectra, and elemental analysis.

Encouraged by this result, the reactions of various other amine combinations were also investigated in a similar manner and a small library of compounds **5h–r** were accomplished. The successful results are summarized in Table 3 and all the products are fully characterized by IR, ^{1}H, and ^{13}C NMR as well as elemental analysis. As a matter of fact, the desirable substituted dihydro-2-oxypyrrole derivatives can be obtained by changing the sequence of addition of amine with dimethyl acetylenedicarboxylate due to the formation of selective hydroamination product (Table 3, entry 11). Moreover, the structure of **5o** was confirmed by X-ray crystallography as shown in Figure 2.[18]

A plausible mechanism for the formation of dihydro-2-oxypyrrole was proposed. Initially the amine reacts with formaldehyde and DMAD to form the imine **A** and hydroamination intermediate **B**, respectively. The intermediate **B** undergoes Mannich type reaction with activated imine **A** in the presence of molecular iodine leading to the formation of intermediate **C**. The intermediate **C** can also exist in other possible resonating structure **D**. The intermediate **C** undergoes concomitant cyclization via intramolecular nucleophilic reaction giving adduct **E**, which finally tautomerizes to the desired dihydro-2-oxypyrrole derivatives **5** as shown in Scheme 2. Similarly, the intermediate D may also react with another molecule of formaldehyde to give pyrimidine derivatives **6**, which is reported by us in the presence of silica supported perchloric acid.[19] We did not observe for the formation of compound **6** because molecular iodine acts as Lewis acid.

In summary, we have demonstrated a mild and efficient iodine catalyzed synthesis of functionalized dihydro-2-oxypyrroles using one-pot four-component reactions of DMAD, amines, and formaldehyde. However, we have not obtained pyrimidine under the experimental conditions. The significant advantages of present protocol are simple experimental procedure, non-toxic by-product, high atom-economy, good yields, and use of eco-friendly, cost-effective catalyst. The new heterocyclic entities containing β-amino acid skeleton might exhibit interesting pharmacological activities.

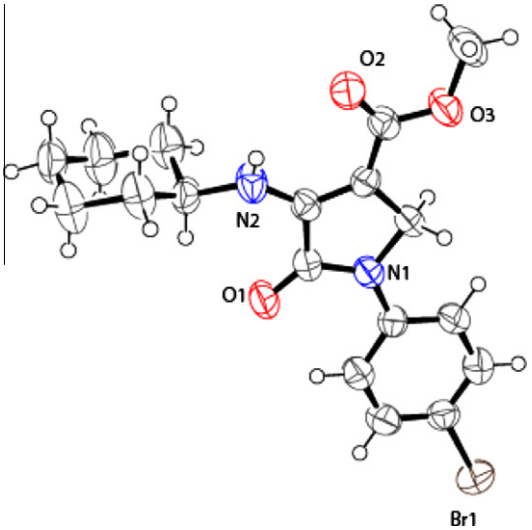


Figure 2. X-ray crystal structure of compound **5o** (CCDC No. 856176).

Acknowledgements

A.G. is thankful to the CSIR, New Delhi for providing research fellowship. We acknowledge DST, New Delhi for providing single crystal XRD facility to the Department of Chemistry under FIST program (S. No.: SR/FST/CSII-007/2003). We are thankful to the referees for their valuable comments and suggestions.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.03.046.

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17. *Typical procedure for dihydro-2-oxopyrroles* ***5a***: Into a 25 mL of round-bottomed flask was taken DMAD (0.142 g, 1.0 mmol) in methanol (3 mL). Then, aniline (0.093 g, 1 mmol) was added into it. The reaction mixture was stirred for 10 min. After that aniline (0.093 g, 1 mmol), formaldehyde (1.5 mmol) and iodine (10 mol %) were added successively. Then the reaction mixture was kept for stirring at room temperature until the reaction was complete, which was monitored by TLC. The solid precipitate appeared at the end of the reaction, which was filtered through a Büchner funnel. The product was washed with 1 mL of ethanol to remove unreacted starting materials. The pure product was obtained after recrystallization from ethanol.
Methyl 2,5-dihydro-5-oxo-1-phenyl-4-(phenylamino)-1H-pyrrole-3-carboxylate (***5a***): White solid: mp 155–156 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.73 (s, 3H), 4.54 (s, 2H), 7.14 (d, J = 8.4 Hz,2H), 7.19 (t, J = 7.6 Hz, 2H), 7.32 (t, J = 7.6 Hz, 2H), 7.39 (t, J = 7.6 Hz, 2H), 7.78 (d, J = 8.4 Hz, 2H), 8.01 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 48.36, 51.39, 103.03, 119.30, 122.86, 124.71, 125.16, 128.43, 129.24, 138.78, 142.98, 163.91, 164.85; IR (KBr, cm^{-1}): 3269, 1692, 1646; Anal Calcd. $C_{18}H_{16}N_2O_3$ (308.33): requires C, 70.12; H, 5.23; N, 9.09. Found: C, 70.10; H, 5.20; N,9.01.
Methyl 1-(4-bromophenyl)-4-(cyclohexylamino)-5-oxo-2,5-dihydro-1H-pyrrole-3-carboxylate (***5o***): Yellow solid: mp 123–124 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.15–1.27 (m, 3H), 1.37–1.46 (m, 3H), 1.61–1.68 (m, 1H), 1.73–1.77 (m, 2H), 1.99–2.02 (m, 2H), 3.79 (s, 3H), 4.37 (s, 2H), 4.57 (s, 1H), 7.49 (d, J = 8.8 Hz, 2H), 7.67 (d, J = 8.8 Hz, 2H); 13C NMR (100 MHz, CDCl3): δ 24.81, 25.62, 34.89, 47.95, 51.14, 95.92, 117.89, 120.73, 132.17, 138.02, 164.51, 165.62; IR (KBr, cm-1): 3309, 1700, 1631; Anal Calcd. $C_{18}H_{21}BrN_2O_3$ (392.07): requires C, 54.97; H, 5.38; N, 7.12. Found: C, 54.88; H, 5.28; N, 7.03.
18. Complete crystallographic data of 5o for the structural analysis has been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 856176. Copies of this information may be obtained free of charge from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-1223-336033, e-mail: deposit@ccdc.cam.ac.uk or via: www.ccdc.cam.ac.uk).
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