A New Approach to the Preparation of 1,3,4-Triarylpyrroles

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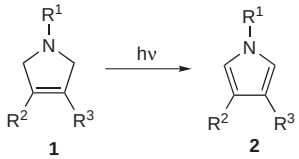
Abstract: A class of 1,3,4-triaryl-2,5-dihydropyrroles were synthesized using the McMurry coupling reaction as the key step. The non-catalytic photoconversion of 1,3,4-triaryl-2,5-dihydropyrroles furnished 1,3,4-triarylpyrroles in good yields (63–89%). It was found that the photoconversion was facile and very reliable; the solvent was found to play an important role.

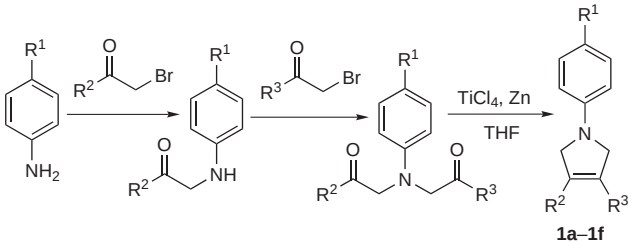
Key words: 1,3,4-triaryl-2,5-dihydropyrrole, 1,3,4-triarylpyrrole, photoconversion, McMurry reaction

Synthesis of 1,3,4-trisubstituted pyrroles is an attractive area in heterocyclic chemistry due to the fact that many pyrroles are subunits of natural products,[1] pharmaceutical drugs,[2] and agrochemicals.[3] In particular, 3,4-disubstituted pyrroles have generated considerable interest owing to their remarkable diversity of biological activity.[4] A number of these compounds have been shown to possess antidiabetic, fungicidal, herbicidal, or antibacterial properties. However, it is also noteworthy that the 3,4-disubstituted pyrrole system is probably the most difficult to obtain: selective substitutions at one or more of the β-positions are a challenge because of the tendency of this pyrrole system to undergo aromatic substitution reactions at the more electronically favorable α-position of the heterocyclic ring. There are many methodologies for the preparation of 3,4-disubstituted pyrroles: 1) coupling of imines and nitroalkanes;[5] 2) Friedel–Crafts acylation with an electron-withdrawing group on the pyrrole nitrogen;[6] 3) from 3,4-silylated precursors;[7] 4) from Michael acceptors with tosylmethyl isocyanide (TOSMIC);[8] 5) by palladium-catalyzed cyclization of amino allenes;[9] 6) by reduction of 3-and 4-pyrrolin-2-ones with 9-BBN;[10] 7) by multicomponent coupling reactions;[11] and 8) many other methods.[12] In this communication, we present a new approach to the preparation of 1,3,4-triarylpyrroles by simple non-catalytic photoconversion of 1,3,4-triaryl-2,5-dihydropyrroles (Scheme 1). It was found that the photoconversion was facile and very reliable.



Scheme 1

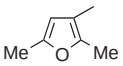
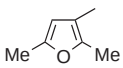
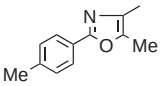
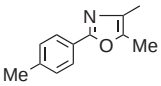
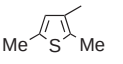
1,3,4-Triaryl-2,5-dihydropyrroles **1a**–**f**[13] were prepared according to the synthetic route shown in Scheme 2 by employing the McMurry coupling reaction as the key step.



Scheme 2

When both substituents R^2 and R^3 were same, the first two steps could be combined in one reaction just by changing the ratio of 2-bromoacetophenone or other 2-bromoacetone derivatives and aniline derivatives from 1:1 to 2:1. The last coupling reaction offered excellent yield whether the substituents were the same or not (Table 1).

Table 1 1,3,4-Triaryl-2,5-dihydropyrroles **1a**–**f**

Compd	R^1	R^2	R^3	Yield (%)
1a	H			74
1b	OMe			85
1c	Cl			66
1d	OMe			80
1e	OMe			78
1f	OMe			61

1,3,4-Triarylpyrroles **2a**–**f**[14] were produced by simple non-catalytic photoconversion of 1,3,4-triaryl-2,5-dihydropyrroles **1a**–**f** in solution. Irradiating a solution of **1a** in acetonitrile with UV light (high-pressure Hg lamp, 500 W) produced **2a** in an excellent yield of 84%. The chemical structure of **2a** was identified by ^{1}H NMR spectroscopy and MS analysis. It was found that the typical signal at 4.57 ppm arising from the 2,5-dihydropyrrole bridging unit of **1a** disappeared and a new signal at low field

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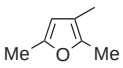
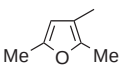
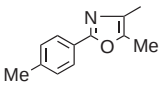
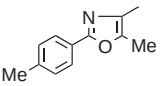
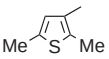
appeared in the ^{1}H NMR spectrum of **2a**, which corresponded to protons on the pyrrole ring. Furthermore, the mass spectra of **1a** and **2a** showed the relative abundance of both molecular ion peaks (**1a** *m*/*z* = 297, **2a** *m*/*z* = 295) was 100%. In addition to the above evidence, the absorption maximum band of **2a** (λ_{max} = 270 nm, MeCN) was red shifted by as much as 28 nm compared to that of **1a** (λ_{max} = 242nm, MeCN). Similar results were obtained when other compounds **1b**–**f** were irradiated with UV light in acetonitrile, and 1,3,4-triarylpyrroles **2b**–**f** were obtained in good yields (Tables 2, 63ndash;89%), indicating that the photoconversion was facile and very reliable.

Table 2 1,3,4-Triarylpyrroles **2a**–**f**

Compd	R^1	R^2	R^3	Yield (%)
2a	H			84
2b	OMe			89
2c	Cl			63
2d	OMe			76
2e	OMe			73
2f	OMe			70

The solvent was found to play an important role in the photoconversion although the mechanism is not clear. Solvents such as $CHCl_3$, CH_2Cl_2, and CH_3CN were excellent for the photoconversion. While the photoconversion could also be accomplished in THF and toluene, longer irradiation times were required. When hexane or cyclohexane was employed as solvent, the photoconversion was unsuccessful.

Oxygen also played a role in the photoconversion of 1,3,4-triaryl-2,5-dihydropyrroles to 1,3,4-triarylpyrroles in solution. It was found that oxygen increased, on the one hand, the velocity of the photoconversion, resulting in a shorter reaction time, but on the other hand the yield decreased. Take for example **2c**, in acetonitrile (1×10^{-4} M) the reaction took five minutes in the presence of oxygen, eight minutes in the presence of air, and 12 minutes in the presence of nitrogen with yields of 51%, 63%, and 70%, respectively. Other compounds showed similar results. This suggests that the yield from the photoconversion could be increased by irradiating in an atmosphere of nitrogen gas.

In conclusion, a facile and reliable synthetic approach to the preparation of 1,3,4-triarylpyrroles from 1,3,4-triaryl-2,5-dihydropyrroles has been developed. The simple procedure, good yield, and absence of catalyst are advantages of this reaction.

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References and Notes

(1) Amima, R.; Evan, T.; Aknin, N.; Kashman, Y. *J. Nat. Prod.* **2000**, *63*, 832.
(2) (a) Unverferth, K.; Engel, J.; Hofgen, N.; Rostock, A.; Gunther, R.; Lankau, H. J.; Menzer, M.; Rolfs, A.; Liebscher, L.; Muller, B. *J. Med. Chem.* **1998**, *41*, 63. (b) Dannhardt, G.; Kiefer, W.; Kramer, G.; Maehrlein, S.; Nowe, U.; Fiebich, B. *Eur. J. Med. Chem.* **2000**, *35*, 499.
(3) (a) Jacobi, P. A.; Coults, L. D.; Guo, J. S.; Leung, S. L. *J. Org. Chem.* **2000**, *65*, 205. (b) Boger, D. L.; Boyce, C. W.; Labrili, M. A.; Sehon, C. A.; Jin, Q. *J. Am. Chem. Soc.* **1999**, *121*, 54.
(4) (a) Holland, G. F. U. Patent 4,282,242, **1981**; *Chem. Abstr*. **1981**, *95*, 187068e. (b) Koho, K. T. (Nippon Soda Co., Ltd.) JP 81 79,672, **1981**; *Chem. Abstr*. **1981**, *95*, 187069f. (c) Bettarini, F.; Meazza, G.; Castoro, P.; Portoso, D. Patent PCT Int. Appl. WO 02 70476, **2002**; *Chem. Abstr*. **2002**, *137*, 232545. (d) Umio, S.; Kariyone, K. JP 68 14,699, **1968**; *Chem. Abstr*. **1969**, *70*, 87560z.
(5) Shiraishi, H.; Nishitani, T.; Nishihara, T.; Sakaguchi, S.; Ishii, Y. *Tetrahedron* **1999**, *55*, 13957.
(6) Zelikin, A.; Shastri, V. R.; Langer, R. *J. Org. Chem.* **1999**, *64*, 3379.
(7) Liu, J.-H.; Chan, H.-W.; Wong, H. N. *J. Org. Chem.* **2000**, *65*, 3274.
(8) (a) Airaksinen, A. J.; Ahlgren, M.; Vepsalainen, J. *J. Org. Chem.* **2002**, *67*, 5019. (b) Smith, N. D.; Huang, D.; Cosford, N. D. P. *Org. Lett.* **2002**, *4*, 3537.
(9) Dieter, R. K.; Yu, H. *Org. Lett.* **2001**, *3*, 3855.
(10) Verniest, G.; De Kimpe, N. *Synlett* **2003**, 2013.
(11) (a) Balme, G. *Angew. Chem. Int. Ed.* **2004**, *43*, 6238. (b) Dhawan, R.; Arndtsen, B. A. *J. Am. Chem. Soc.* **2004**, *126*, 468.
(12) (a) De Kimpe, N.; Tehrani, K. A.; Stevens, C.; De Cooman, P. *Tetrahedron* **1997**, *53*, 3693. (b) Tehuani, K. A.; Borremans, D.; De Kimpe, N. *Tetrahedron* **1999**, *55*, 4133. (c) Verniest, G.; Claessens, S.; De Kimpe, N. *Tetrahedron* **2005**, *61*, 4631. (d) Verniest, G.; Claessens, S.; Bombeke, F.; Van Thienen, T.; De Kimpe, N. *Tetrahedron* **2005**, *61*, 2879. (e) Keppens, M.; De Kimpe, N.; Fonck, G. *Synth. Commun.* **1996**, *26*, 3097.
(13) **1a–f; General Procedure** 2-Bromoacetophenone or 2-bromoacetone derivative (20 mmol), Na_2CO_3 (20 mmol), and *p*-anisidine (10 mmol) or aniline derivatives (10 mmol) were dissolved in EtOH (95 %; 20 mL). The mixture was stirred for 0.5 h at ambient temperature followed by heating to reflux for 4 h. The reaction mixture was cooled and diluted with H_2O. The solid was obtained and purified by recrystallization from EtOH. To a suspension of Zn powder (0.3 mol) in THF (350 mL) under nitrogen flux was added $TiCl_4$ (10 mL) at 0 °C by syringe. The mixture was then refluxed for 1 h. To the mixture was added the solid (15 mmol) obtained above in THF (250 mL) very slowly at ambient temperature. The reaction mixture was stirred for another 24 h in darkness then quenched with K_2CO_3 (40%; 80 mL). The solid was filtered and washed with Et_2O (50 mL). The combined organic phases were concentrated to 50 mL under reduced pressure. H_2O (50 mL) was then added to the residue. The product was extracted with Et_2O (50 mL) and dried over $MgSO_4$. After evaporation of the solvent, the crude product was purified by flash column

chromatography. For **1f** 2-bromoacetonephenone was treated with *p*-anisidine first, followed by reaction with 3-(2,5-dimethyl)-1′-bromoacetylthiophene. **1a**: ^{1}H NMR: δ = 7.30–7.19 (m, 12 H), 6.66 (d, 3 H, *J* = 7.6 Hz), 4.57 (s, 4 H). MS (EI): *m*/*z* = 297 (M^+, 100). HRMS: *m*/*z* calcd for $C_{22}H_{19}N$ [M^+]: 297.3991; found: 297.4056. **1b**: ^{1}H NMR: δ = 7.30–7.27 (m, 10 H), 6.88 (d, 2 H, *J* = 8.8 Hz), 6.63–6.60 (d, 2 H, *J* = 8.9 Hz), 4.54 (s, 4 H), 3.69 (s, 3 H). MS (EI): *m*/*z* = 327 (M^+, 100). HRMS: *m*/*z* calcd for $C_{23}H_{21}NO$ [M^+]: 327.4259; found: 327.6128. **1c**: ^{1}H NMR: δ = 7.30–7.27 (m, 10 H), 7.22 (d, 2 H, *J* = 8.2 Hz), 6.67 (d, 2 H, *J* = 8.8 Hz), 4.57 (s, 4 H). MS (EI): *m*/*z* = 330 (M^+ – 1, 99), 138 (100). HRMS: *m*/*z* calcd for $C_{22}H_{18}ClN$ [M^+]: 331.8542; found: 332.0014. **1d**: ^{1}H NMR: δ = 6.92 (d, 2 H, *J* = 9.0 Hz), 6.57 (d, 2 H, *J* = 6.0 Hz), 5.87 (s, 2 H), 4.35 (s, 4 H), 3.79 (s, 3 H), 2.24 (s, 6 H), 2.06 (s, 6 H). MS (EI): *m*/*z* = 363 (M^+, 100). HRMS: *m*/*z* calcd for $C_{23}H_{25}NO_3$ [M^+]: 363.5225; found: 363.5249. **1e**: ^{1}H NMR: δ = 7.93 (d, 4 H, *J* = 9.0 Hz), 7.28 (d, 4 H, *J* = 9.0 Hz), 6.93 (d, 2 H, *J* = 9.0 Hz), 6.68 (d, 2 H, *J* = 9.0 Hz), 4.64 (s, 4 H), 3.79 (s, 3 H), 2.41 (s, 6 H), 2.06 (s, 6 H). MS (EI): *m*/*z* = 517 (M^+, 52), 119 (100). HRMS: *m*/*z* calcd for $C_{33}H_{31}N_3O_3$ [M^+]: 517.6259; found: 517.6164. **1f**: ^{1}H NMR: δ = 7.30–7.25 (m, 5 H), 6.88 (d, 2 H, *J* = 9.0 Hz), 6.68 (s, 1 H), 6.62 (d, 2 H, *J* = 9.0 Hz), 4.59 (t, 2 H, *J* = 4.5 Hz), 4.36 (t, 2 H, *J* = 4.5 Hz), 3.71 (s, 3 H), 2.41 (s, 3 H), 1.95 (s, 3 H). MS (EI): *m*/*z* = 361 (M^+, 100). HRMS: *m*/*z* calcd for $C_{23}H_{23}NOS$ [M^+]: 361.5067; found: 361.5095.

(14) **2a–f; General Procedure** A solution of 1,3,4-trisubstituted 2,5-dihydropyrroles (0.5 mmol) in CH_2Cl_2 (100 mL) was irradiated with UV light (high-pressure Hg lamp, 500 W) until the starting material was no longer detected by TLC. After the solvent was evaporated the crude product were purified by column chromatography (EtOAc–PE). **2a**: ^{1}H NMR: δ = 7.71 (d, 2 H, *J* = 7.7 Hz), 7.53 (d, 2 H, *J* = 7.4 Hz), 7.48 (s, 2 H), 7.34–7.21 (m, 11 H). MS (EI): *m*/*z* = 295 (M^+, 100). HRMS: *m*/*z* calcd for $C_{22}H_{17}N$ [M^+]: 295.3833; found: 295.4122. **2b**: ^{1}H NMR: δ = 7.57 (d, 2 H, *J* = 9.0 Hz), 7.32–7.17 (m, 12 H), 7.05 (d, 2 H, *J* = 8.8 Hz), 3.81 (s, 3 H). MS (EI): *m*/*z* = 325 (M^+, 100). HRMS: *m*/*z* calcd for $C_{23}H_{19}NO$ [M^+]: 325.4101; found: 325.4708. **2c**: ^{1}H NMR: δ = 7.72 (d, 2 H, *J* = 8.8 Hz), 7.52 (d, 2 H, *J* = 8.7 Hz), 7.46 (s, 2 H), 7.31–7.20 (m, 8 H). MS (EI): *m*/*z* = 329 (M^+, 100). HRMS: *m*/*z* calcd for $C_{22}H_{16}ClN$ [M^+]: 329.8384; found: 329.9123. **2d**: ^{1}H NMR: δ = 7.36 (d, 2 H, *J* = 8.8 Hz), 6.98 (d, 2 H, *J* = 9.0 Hz), 6.94 (s, 2 H), 5.86 (s, 2 H), 3.85 (s, 3 H), 2.25 (s, 6 H), 2.18 (s, 3 H). MS (EI): *m*/*z* = 361 (M^+, 100). HRMS: *m*/*z* calcd for $C_{23}H_{23}NO_3$ [M^+]: 361.4387; found: 361.4401. **2e**: ^{1}H NMR: δ = 7.96 (d, 4 H, *J* = 9.0 Hz), 7.45 (d, 2 H, *J* = 9.0 Hz), 7.32 (s, 2 H), 7.27 (d, 4 H, *J* = 8.9 Hz), 7.00 (d, 2 H, *J* = 8.9 Hz), 3.85 (s, 3 H), 2.41 (s, 6 H), 2.12 (s, 6 H). MS (EI): *m*/*z* = 515 (M^+, 65), 119 (100). HRMS *m*/*z* calcd for $C_{33}H_{29}N_3O_3$ [M^+]: 515.6106; found: 515.6164. **2f**: ^{1}H NMR: δ = 7.43–7.30 (m, 6 H), 7.25–7.23 (m, 2 H), 7.02–7.00 (m, 3 H), 6.57 (s, 1 H), 3.87 (s, 3 H), 2.45 (s, 3 H), 2.22 (s, 3 H). MS (EI): *m*/*z* = 359 (M^+, 100). HRMS: *m*/*z* calcd for $C_{23}H_{21}NOS$ [M^+]: 359.4909; found: 359.4972.