DOI 10.1007/s10593-018-2335-6

Chemistry of Heterocyclic Compounds **2018**, *54*(7), 700–702

One-pot synthesis of [4-(*tert*-butyl)-1*H*-pyrrol-3-yl](phenyl)methanone from tosylmethyl isocyanide and carbonyl compound

Ramandeep Kaur[1], Kapil Kumar[2,3]*

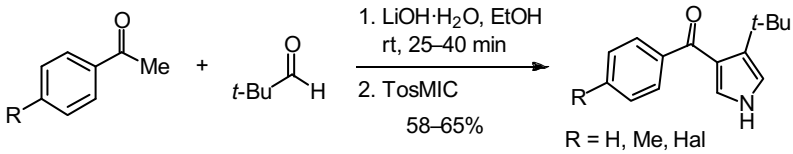
[1] *Department of Pharmaceutical Chemistry, Indo-Soviet Friendship College of Pharmacy (ISFCP), Moga, Punjab-142001, India; e-mail: rmnkaur30@gmail.com*

[2] *School of Pharmaceutical Sciences, Apeejay Stya University, Sohna-Palwal Road, Sohna, Gurgaon, Haryana-122103, India; e-mail: kapil.py@gmail.com*

[3] *National Institute of Pharmaceutical Education and Research, Sector-67, S.A.S. Nagar, Mohali, Punjab-160062, India*

Published in Khimiya Geterotsiklicheskikh Soedinenii, 2018, *54*(7), 700–702

Submitted March 21, 2018
Accepted June 18, 2018



An efficient one-pot synthetic procedure for [4-(*tert*-butyl)-1*H*-pyrrol-3-yl](phenyl)methanone was elaborated using acetophenone and trimethylacetaldehyde in the presence of TosMIC and mild base LiOH·H_2O. This method is very economical for the synthesis of pyrrole derivatives and was successfully utilized with good yields.

Keywords: lithium hydroxide, pyrrole, TosMIC, cycloaddition.

Pyrrole is considered to be a priviledged heterocycle because of its therapeutic importance including antibacterial,[1] antifungal,[2] antiviral,[3] anti-inflammatory,[4] and anticancer[5] activities. It is an important structural moiety found in complex macromolecules comprising porphyrins of heme, chlorins, bacteriochlorins, chlorophyll, porphyrinogens.[6–8] It has also been found to be an important core unit for many biologically active molecules such as tolmetin, atorvastatin, chlorfenapyr, premazepam, pyrvinium, roseophilin.[8] Therefore, pyrrole cycle is an imperative structural framework found in a wide range of biologically active natural products and pharmaceutically active agents.[9,10] Synthesis of various substituted pyrroles always poses a serious problem due to functional group complexity and stability issues. Among various methods, few important strategies are employed for the synthesis of pyrrole derivatives such as: a) condensation reaction of α-aminocarbonyl compounds with activated ketones (Knorr pyrrole synthesis);[8,9,11] b) reactions of α-halocarbonyl compounds with β-keto esters and ammonia (Hantzsch pyrrole synthesis);[12] c) reaction of 1,4-dicarbonyl compounds with primary amines (Paal–Knorr synthesis).[10,13] Pyrrole chemical transformations mainly include electrophilic substitution because of the presence of lone pair of electrons on the nitrogen and consequent stability of σ-complexes.[14,15] *p*-Tosylmethyl isocyanide (TosMIC) (Fig. 1) has atypical structure and reactivity which had been discussed for more than four decades. It is considered to be the most versatile synthon derived from methyl isocyanide exhibiting a multifaceted chemistry that is of great utility in organic synthesis.[16–18]

TosMIC has been a noteworthy invention since a number of valuable intermediates like oxazole and oxazoline, imidazole, 1,2,4-triazole, thiazole, ketones, and α-hydroxyaldehydes can be synthesized from a single synthon. The transformation includes a dipolar [1,3] cycloaddition reaction involving base-induced 1,3-dipole formation followed by reaction with dipolarophile to form a five-membered heterocycle which can be custom-made to an assortment of constructive intermediates. Despite the adaptability of this method to various heterocycles, we found very restricted literature on the synthesis of pyrrole derivatives. The bases which are generally used are sodium hydride, potassium

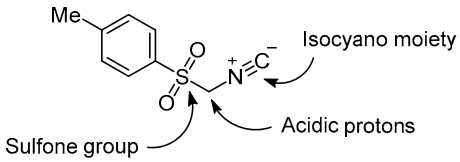
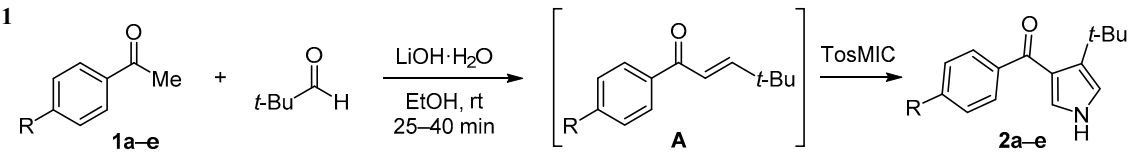


Figure 1. Structure of *p*-tosylmethyl isocyanide.

Scheme 1



tert-butoxide, etc. Despite ensuring reasonable yield these bases typically necessitate anhydrous conditions and inert atmosphere. Thus there has been stern requirement to develop conditions which can be apposite for environment as well as industrial scale-up.[19]

Based on our interest on heterocyclic chemistry and development of synthetic methodologies,[20–22] our aim was to develop an efficient approach for the synthesis of 3,4-disubstituted pyrroles. Previously, we synthesized pyrrole derivatives using TosMIC and aromatic aldehydes[20f] or aliphatic aldehydes containing α-hydrogen.[21b] It has been established that $LiOH·H_2O$ in ethanol can work as efficient base for the synthesis of chalcone which is formed as the intermediate in this reaction. Since it was not essential to use sturdy base for deprotonation of TosMIC that was apparent from synthesis of imidazole, oxazole, and triazole derivatives, we thought of using $LiOH·H_2O$ for the [2+3] cycloaddition reaction involving TosMIC and α,β-unsaturated compound in which potassium carbonate has been generally used. Therefore, we made an attempt to carry out one-pot synthesis by stirring a mixture of acetophenones **1a**–**e**, trimethylacetaldehyde, $LiOH·H_2O$ in ethanol at room temperature. This led to the formation of chalcone **A** which further reacted with TosMIC. The reaction was carefully monitored using TLC. It was observed that initially chalcone tended to dissolve and soon after that pyrrole derivatives were formed. The precipitates formed were filtered and washed with water. Analysis of the precipitated solids revealed that (aryl)[4-(*tert*-butyl)-1*H*-pyrrol-3-yl]methanones **2a**–**e** have been formed (Scheme 1).

Various substituted acetophenones were tested to generalize the scope of reaction and affordable yields were obtained in all the cases (Table 1). The reaction rates were faster and good yields were obtained with acetophenones containing electron-deficient aromatic cycles in comparison to electron-rich cycles which took more reaction time and gave moderate yields.

Thus, the above strategy afforded (aryl)[4-(*tert*-butyl)-1*H*-pyrrol-3-yl]methanones with reasonably good yields in a one-pot reaction using lithium hydroxide as a base and inexpensive reagent *p*-tosylmethyl isocyanide.

Experimental

^1H and ^{13}C NMR spectra were registered on a Bruker spectrometer (400 and 100 MHz, respectively) in $CDCl_3$, internal standard TMS. High-resolution mass spectra were registered on a Oracle spectrometer, using electrospray ionization. Melting points were determined on a Mettler Toledo apparatus. Column chromatography was performed on silica gel (60–120 mesh) using EtOAc–hexane mixture (3:7) as eluent. TLC was performed on Merk TLC plates, eluent EtOAc–hexane, 1:10, visualization by UV light.

Table 1. Reaction time and yields of (aryl)[4-(*tert*-butyl)-1*H*-pyrrol-3-yl]methanones **2a**–**e**

Compound	R	Total reaction time, min	Yield, %
2a	H	35	62
2b	Me	40	58
2c	Br	30	65
2d	Cl	27	64
2e	F	25	64

Synthesis of [4-(*tert*-butyl)-1*H*-pyrrol-3-yl](aryl)methanones 2a–e (General method). A mixture of trimethylacetaldehyde (86 mg, 1.0 mmol), acetophenone **1a**–**e** (1.0 mmol), and $LiOH·H_2O$ (4 mg, 0.1 mmol) in EtOH (3 ml) was stirred at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, $LiOH·H_2O$ (46 mg, 1.1 mmol) and TosMIC (215 mg, 1.1 mmol) were added. Initially, chalcone dissolved and shortly thereafter pyrrole derivative was formed. Reaction was monitored by TLC. Once reaction got completed, water (10 ml) was added and the product was extracted with EtOAc (2×10 ml). Organic layer was dried using Na_2SO_4 and evaporated under reduced pressure. The product was isolated from the crude mixture by column chromatography on silica gel (60–120 mesh) using EtOAc–hexane mixture as eluent. Pyrrole derivatives **2a**–**e** were obtained in a form of white solids, yields are given in Table 1.

[4-(*tert*-Butyl)-1*H*-pyrrol-3-yl](phenyl)methanone (2a). Mp 186–188°C. ^1H NMR spectrum, δ, ppm: 8.42 (1H, br. s, NH); 7.76–7.74 (2H, m, H Ph); 7.52–7.39 (3H, m, H Ph); 7.02–7.01 (1H, s, H pyrrole); 6.67–6.66 (1H, s, H pyrrole); 1.57 (9H, s, $C(CH_3)_3$). ^{13}C NMR spectrum, δ, ppm: 192.5; 141.8; 136.5; 131.1; 129.6; 129.3; 127.9; 122.4; 116.2; 31.6; 30.6. Found, *m*/*z*: 250.1208 $[M+Na]^+$. $C_{15}H_{17}NNaO$. Calculated, *m*/*z*: 250.1208.

[4-(*tert*-Butyl)-1*H*-pyrrol-3-yl](4-methylphenyl)methanone (2b). Mp 164–166°C. ^1H NMR spectrum, δ, ppm: 8.42 (1H, br. s, NH); 7.68–7.66 (2H, m, H Ar); 7.26–7.20 (2H, m, H Ar); 7.00–6.99 (1H, m, H pyrrole); 6.65–6.64 (1H, m, H pyrrole); 2.41 (3H, s, CH_3); 1.42 (9H, s, $C(CH_3)_3$). ^{13}C NMR spectrum, δ, ppm: 192.5; 141.6; 139.0; 136.3; 129.5; 129.1; 128.6; 122.4; 116.1; 31.6; 30.7; 21.5. Found, *m*/*z*: 264.1368 $[M+Na]^+$. $C_{16}H_{19}NNaO$. Calculated, *m*/*z*: 264.1364.

(4-Bromophenyl)[4-(*tert*-butyl)-1*H*-pyrrol-3-yl]methanone (2c). Mp 162–164°C. ^1H NMR spectrum, δ, ppm: 8.48 (1H, br. s, NH); 7.63–7.54 (4H, m, H Ar); 6.98 (1H, s, H pyrrole); 6.66 (1H, s, H pyrrole); 1.41 (9H, s, $C(CH_3)_3$). ^{13}C NMR spectrum, δ, ppm: 191.2; 140.6; 136.6; 131.1; 130.8; 129.6; 125.8; 122.1; 116.4; 31.6; 30.5. Found, *m*/*z*: 328.0316 $[M+Na]^+$. $C_{15}H_{16}BrNNaO$. Calculated, *m*/*z*: 328.0313.

[4-(*tert*-Butyl)-1*H*-pyrrol-3-yl](4-chlorophenyl)methanone (2d). Mp 176–178°C. ^{1}H NMR spectrum, δ, ppm: 8.45 (1H, br. s, NH); 7.70–7.68 (2H, m, H Ar); 7.40–7.38 (2H, m, H Ar); 6.99–6.98 (1H, m, H pyrrole); 6.67–6.66 (1H, m, H pyrrole); 1.41 (9H, s, $C(CH_3)_3$). ^{13}C NMR spectrum, δ, ppm: 191.1; 140.1; 137.3; 136.6; 130.6; 129.5; 128.2; 122.1; 116.4; 31.6; 30.5. Found, *m*/*z*: 284.0815 $[M+Na]^+$. $C_{15}H_{16}ClNNaO$. Calculated, *m*/*z*: 284.0818.

[4-(*tert*-Butyl)-1*H*-pyrrol-3-yl](4-fluorophenyl)methanone (2e). Mp 214–216°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.42 (1H, br. s, NH); 7.80–7.76 (2H, m, H Ar); 7.11–7.07 (2H, m, H Ar); 7.00–6.98 (1H, m, H pyrrole); 6.67 (1H, t, *J* = 2.3, H pyrrole); 1.42 (9H, s, $C(CH_3)_3$). ^{13}C NMR spectrum, δ, ppm: 191.1; 165.9; 163.4; 137.9; 136.5; 131.7; 129.1; 122.3; 116.3; 115.0; 114.8; 31.6; 30.6. Found, *m*/*z*: 268.1112 $[M+Na]^+$. $C_{15}H_{16}FNNaO$. Calculated, *m*/*z*: 268.1114.

References

1. (a) Sbardella, G.; Mai, A.; Artico, M.; Loddo, R.; Setzu, M. G.; La Colla, P. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1537. (b) Raimondi, M. V.; Cascioferro, S.; Schillaci, D.; Petruso, S. *Eur. J. Med. Chem.* **2006**, *41*, 1439. (c) Biava, M.; Porretta, G. C.; Poce, G.; Deidda, D.; Pompei, R.; Tafi, A.; Manetti, F. *Bioorg. Med. Chem.* **2005**, *13*, 1221.
2. Di Santo, R.; Tafi, A.; Costi, R.; Botta, M.; Artico, M.; Corelli, F.; Forte, M.; Caporuscio, F.; Angiolella, L.; Palamara, A. T. *J. Med. Chem.* **2005**, *48*, 5140.
3. Bialer, M.; Yagen, B.; Mechoulam, R.; Becker, Y. *J. Med. Chem.* **1980**, *23*, 1144.
4. (a) Dannhardt, G.; Kiefer, W.; Krämer, G.; Maehrlein, S.; Nowe, U.; Fiebich, B. *Eur. J. Med. Chem.* **2000**, *35*, 499. (b) Laufer, S. A.; Augustin, J.; Dannhardt, G.; Kiefer, W. *J. Med. Chem.* **1994**, *37*, 1894. (c) Khanna, I. K.; Weier, R. M.; Yu, Y.; Collins, P. W.; Miyashiro, J. M.; Koboldt, C. M.; Veenhuizen, A. W.; Currie, J. L.; Seibert, K.; Isakson, P. C. *J. Med. Chem.* **1997**, *40*, 1619.
5. (a) Wakabayashi, K.-i.; Imai, K.; Miyachi, H.; Hashimoto, Y.; Tanatani, A. *Bioorg. Med. Chem.* **2008**, *16*, 6799. (b) Lee, H.; Lee, J.; Shin, Y.; Jung, W.; Kim, J.-H.; Park, K.; Ro, S.; Chung, H.-H.; Koh, J. S. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2963.
6. Artico, M; Di Santo, R.; Costi, R.; Massa, S.; Retico, A.; Artico, M.; Apuzzo, G.; Simonetti, G.; Strippoli, V. *J. Med. Chem.* **1995**, *38*, 4223.
7. Tafi, A.; Costi, R.; Botta, M.; Di Santo, R.; Corelli, F.; Massa, S.; Ciacci, A.; Manetti, F.; Artico, M. *J. Med. Chem.* **2002**, *45*, 2720.
8. (a) Harrington, P. E.; Tius, M. A. *Org. Lett.* **1999**, *1*, 649. (b) Sun, H.; Zhang, H.; Ang, E. L.; Zhao, H. *Bioorg. Med. Chem*. **2018**, *26*, 1275. (c) Honey; Thareja, S.; Kumar, M.; Sinha, V. R. *Eur. J. Med. Chem*. **2012**, *53*, 76.
9. Rapoport, H.; Harbuck, J. W. *J. Org. Chem.***1971**, *36*, 853.
10. Amarnath, V.; Anthony, D. C.; Amarnath, K.; Valentine, W. M.; Wetterau, L. A.; Graham, D. G. *J. Org. Chem.* **1991**, *56*, 6924.
11. (a) Knorr, L. *Ber. Dtsch. Chem. Ges*. **1884**, *17*, 1635. (b) Knorr, L. *Justus Liebigs Ann. Chem.* **1886**, *236*, 290. (c) Cheng, L.; Lightner, D. A. *Synthesis* **1999**, 46. (d) Lavecchia, A.; Costi, R.; Artico, M.; Miele, G.; Novellino, E.; Bergamini, A.; Crespan, E.; Maga, G.; Di Santo, R. *ChemMedChem* **2006**, *1*, 1379.
12. (a) Hantzsch, A. *Ber.* **1890**, *23*, 1474. (b) Feist, F. *Ber.* **1902**, *35*, 1537. (c) Trautwein, A. W.; Süßmuth, R. D.; Jung, G. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2381. (d) Roomi, M. W.; MacDonald, S. F. *Can. J. Chem.* **1970**, *48*, 1689.
13. (a) Paal, C. *Ber.* **1885**, *18*, 367. (b) Knorr, L. *Ber.* **1885**, *18*, 299. (c) Minetto, G.; Raveglia, L. F.; Sega, A.; Taddei, M. *Eur. J. Org. Chem.* **2005**, 5277. (d) Rao, H. S. P.; Jothilingam, S.; Scheeren, H. W. *Tetrahedron* **2004**, *60*, 1625.
14. (a) Garabatos-Perera, J. R.; Rotstein, B. H.; Thompson, A. *J. Org. Chem.* **2007**, *72*, 7382. (b) *The Chemistry of Pyrroles*; Jones, R. A.; Bean, G. P., Eds.; Academic Press: London, 1977, p. 525.
15. Thompson, A.; Butler, R. J.; Grundy, M. N.; Laltoo, A. B. E.; Robertson, K. N.; Cameron, T. S. *J. Org. Chem.* **2005**, *70*, 3753.
16. Van Leusen, A. M.; Hoogenboom, B. E.; Houwing, H. A. *J. Org. Chem.* **1976**, *41*, 711.
17. Possel, O.; Van Leusen, A. M. *Tetrahedron Lett.* **1977**, *18*, 4229.
18. Oldenziel, O. H.; Van Leusen, A. M. *Tetrahedron Lett.* **1974**, *15*, 167.
19. (a) Kumar, V.; Nair, V. A. *Tetrahedron Lett.* **2010**, *51*, 966. (b) Khatik, G. L.; Pal, A.; Mobin, S. M.; Nair, V. A. *Tetrahedron Lett.* **2010**, *51*, 3654. (c) Chouhan, M.; Sharma, R.; Nair, V. A. *Appl. Organomet. Chem.* **2011**, *25*, 470.
20. (a) Chouhan, M.; Kumar, K.; Sharma, R.; Grover, V.; Nair, V. A. *Tetrahedron Lett.* **2013**, *54*, 4540. (b) Goyal, S.; Patel, J. K.; Gangar, M.; Kumar, K.; Nair, V. A. *RSC Adv.* **2015**, *5*, 3187. (c) Kumar, V.; Kumar, K.; Pal, A.; Khatik, G. L.; Nair, V. A. *Tetrahedron* **2013**, *69*, 1747. (d) Kumar, K.; Mudshinge, S. R.; Goyal, S.; Gangar, M.; Nair, V. A. *Tetrahedron Lett.* **2015**, *56*, 1266. (e) Chouhan, M.; Senwar, K. R.; Kumar, K.; Sharma, R.; Nair, V. A. *Synthesis* **2014**, 195. (f) Sharma, R.; Kumar, K.; Chouhan, M.; Grover, V.; Nair, V. A. *RSC Adv.* **2013**, *3*, 14521.
21. (a) Goyal, S.; Patel, B.; Sharma, R.; Chouhan, M.; Kumar, K.; Gangar, M.; Nair, V. A. *Tetrahedron Lett.* **2015**, *56*, 5409. (b) Kumar, K.; More, S. S.; Goyal, S.; Gangar, M.; Khatik, G. L.; Rawal, R. K.; Nair, V. A. *Tetrahedron Lett.* **2016**, *57*, 2315. (c) Kumar, K.; Siddique, J.; Gangar, M.; Goyal, S.; Rawal, R. K.; Nair, V. A. *ChemistrySelect* **2016**, *1*, 2409. (d) Kumar, K.; Konar, D.; Goyal, S.; Gangar, M.; Chouhan, M.; Rawal, R. K.; Nair, V. A. *ChemistrySelect* **2016**, *1*, 3228. (e) Kumar, K.; Konar, D.; Goyal, S.; Gangar, M.; Chouhan, M.; Rawal, R. K.; Nair, V. A. *J. Org. Chem.* **2016**, *81*, 9757. (f) Kumar, K.; More, S. S.; Khatik, G. L.; Rawal, R. K.; Nair, V. A. *J. Heterocycl. Chem.* **2017**, *54*, 2696. (g) Kaur, R.; Manjal, S. K.; Rawal, R. K.; Kumar, K. *Bioorg. Med. Chem.* **2017**, *25*, 4533. (h) Manjal, S. K.; Kaur, R.; Bhatia, R.; Kumar, K.; Singh, V.; Shankar, R.; Kaur, R.; Rawal, R. K. *Bioorg. Chem.* **2017**, *75*, 406.
22. (a) Mittal, M.; Kumar, K.; Anghore, D.; Rawal, R. K. *Curr. Drug Discovery Technol.* **2017**, *14*, 106. (b) Kaur, R.; Chaudhary, S.; Kumar, K.; Gupta, M. K.; Rawal, R. K. *Eur. J. Med. Chem.* **2017**, *132*, 108. (c) Kumar, B.; Singh, V.; Shankar, R.; Kumar, K.; Rawal, R. K. *Curr. Top. Med. Chem.* **2017**, *17*, 148. (d) Talwan, P.; Chaudhary, S.; Kumar, K.; Rawal, R. K. *Curr. Bioact. Compd.* **2017**, *13*, 109. (e) Kaur, R.; Rani, V.; Abbot, V.; Kapoor, Y.; Konar, D.; Kumar, K. *J. Pharm. Chem. Chem. Sci.* **2017**, *1*, 17.