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One-Step Synthesis of 3-Aryl- and 3,4-Diaryl-(1*H*)-Pyrroles Using Tosylmethyl Isocyanide (TOSMIC)

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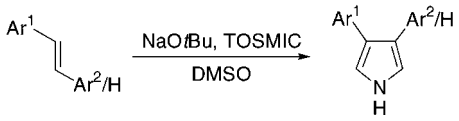
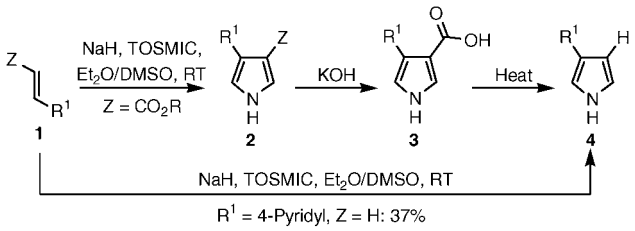
ABSTRACT



A one-step synthesis of 3-aryl and 3,4-diaryl-(1*H*)-pyrroles from TOSMIC and commercially available or readily synthesized arylalkenes is reported. Optimal conditions were found to be NaO*t*Bu in DMSO. The methodology was particularly efficient (yields > 65%) when electron poor aryl groups were attached to the alkene.

The pyrrole ring is an important heterocycle in biological systems being incorporated into the porphyrin ring systems of chlorophyll, heme, Vitamin B_{12}, and the bile pigments. Additionally, there are a number of pyrrole-containing small molecules that exhibit useful biological activities.[1,2] As such, a lot of effort has been spent developing practical methods for the synthesis of pyrrole units that incorporate appropriate functionality.[3] One such method developed by van Leusen is the reaction of tosylmethyl isocyanide (TOSMIC) with a Michael acceptor **1** to generate a 3,4-disubstituted pyrrole **2** (Scheme 1).[4] This procedure necessarily installs the activating Z group of the Michael acceptor at the 3-position of the pyrrole ring formed.[2,4,5]

Scheme 1



Recently, we required a facile and general synthesis of 3-aryl-substituted pyrroles **4** (R^1 = aryl). These 3-aryl pyrroles have typically been accessed via multistep cross-coupling methodology requiring the use of a protecting group for the pyrrole NH[6] or by using van Leusen's TOSMIC

(1) Arima, K.; Imanaka, H.; Kousaka, M.; Fukuta, A.; Tamura, G. *Agr. Biol. Chem.* **1964**, *28*, 575. Nakeno, H.; Umio, S.; Kariyone, K.; Tanaka, K.; Kishimpto, T.; Noguchi, H.; Ueda, I.; Nakamura, H.; Morimoto, Y *Tetrahedron Lett.* **1966**, *7*, 737. Unverferth, K.; Engel, J.; Hofgen, N.; Rostock, A.; Gunther, R.; Lankau, H. J.; Menzer, M.; Rolfs, A.; Liebscher, J.; Muller, B.; Hofmann, H. J. *J. Med. Chem.* **1998**, *41*, 63.

(2) Dannhardt, G.; Kiefer, W.; Kraemer, G.; Maehrlein, S.; Nowe, U.; Fiebich, B. Eur. *J. Med. Chem*. **2000**, *35*, 499. Rango, R.; Marshall, G. R.; Santo, R. D.; Costi, R.; Massa, S.; Rompei, R.; Artico, M. *Bioorg. Med. Chem*. **2000**, *8*, 1423. Artico, M.; Santo, R. D.; Costi, R.; Massa, S.; Retico, A. *J. Med. Chem.* **1995**, *38*, 4223. Magnus, P.; Gallagher, T.; Schultz, J.; Or, Y. S.; Ananthanarayan, T. P. *J. Am. Chem. Soc.* **1987**, *109*, 2706.

(3) Sundberg, R. G. in *Comprehensive Heterocyclic Chemistry*; Katritsky, A. R., Ed.; Pergamon Press: Oxford, 1984; Vol. IV, p 313. Gilchrist, T. L. In *Heterocyclic Chemistry*; Pitman Publishing: London, 1985; Chapters 4 and 6.

(4) van Leusen, A. M.; Siderius, H.; Hoogenboom, B. E.; van Leusen, D. *Tetrahedron Lett.* **1972**, *52*, 5337. Possel, O.; van Leusen, A. M. *Heterocycles* **1977**, *7*, 77. Barton, D. H. R.; Kervagoret, J.; Zard, S. Z. *Tetrahedron* **1990**, *46*, 7587. ten Have, R.; Leusink, F. R.; van Leusen, A. M. *Synthesis* **1996**, 871. Dijkstra, H. P.; ten Have, R.; van Leusen, A. M. *J. Org. Chem*. **1998**, *63*, 5332.

(5) Pavri, N. P.; Trudell, M. L. *J. Org. Chem.* **1997**, *62*, 2649.

(6) Alvarez, A.; Guzman, A.; Ruiz, A.; Velarde, E. *J. Org. Chem.* **1992**, *57*, 1653. Bumagin, N. A.; Nikitina, A. F.; Belatskaya, I. P. *Russ. J. Org. Chem.* **1994**, *30*, 1619.

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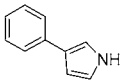
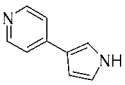
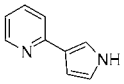
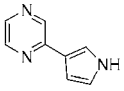
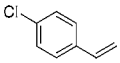
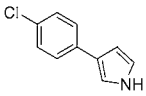
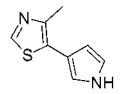
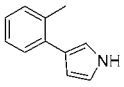
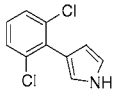
methodology where saponification (**2**→**3**) and decarboxylation (**3**→**4**) are required to remove the ester Z group.[5,7] As a more efficient entry into 3-aryl-pyrroles **4**, we reasoned that electron-deficient vinyl arenes **1** (i.e., R^1 = aryl, Z = H) could act as Michael acceptors, thus negating the need for an electron-withdrawing Z group and so providing 3-aryl pyrroles directly (**1**→**4**). Testing this hypothesis with 4-vinyl pyridine (**1**: R^1 = 4-pyridyl, Z = H), we indeed found that using Et_2O/DMSO as a solvent, we obtained a 37% yield of the desired 3-aryl pyrrole **4** in a single step (Scheme 1).

Further investigation of the factors affecting this transformation using the more challenging substrate styrene led to the optimum conditions of NaO*t*Bu in DMSO. Using these conditions, we investigated the scope of this transformation using a variety of 1-aryl alkenes (Table 1).

Table 1. Synthesis of 3-Aryl Pyrroles Using TOSMIC[a]

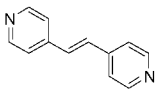
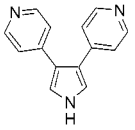
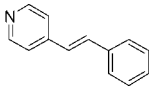
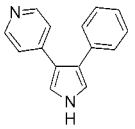
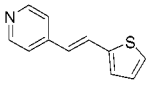
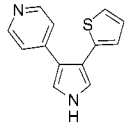
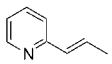
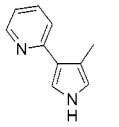
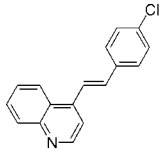
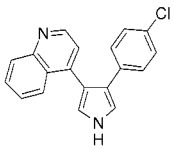
entry	substrate	product	T°C/time	yield[b]
1			50°C/18h	47%
2			25°C/2h	67%
3			25°C/2h	74%
4			25°C/1h	76%
5			50°C/6h	58%
6			50°C/2h	39%
7			75°C/2h	44%
8			100°C/18h	48%

[a] TOSMIC (1.3 equiv), NaO*t*Bu (2 equiv), DMSO, *T* in °C. [b] Isolated yield after chromatography.

In general, higher yields of the desired 3-aryl pyrrole were obtained at lower temperatures and with shorter reaction times when the aryl group of the styrene starting material was more electron deficient. Thus, styrene (entry 1) gave 47% yield after 18 h at 50 °C, while 4-vinyl pyridine (entry 2), 2-vinyl pyridine (entry 3), and 2-vinyl pyrazine (entry 4) all gave good yields (>65%) after only 2 h at 25 °C. As expected, compared to styrene (entry 1), an electron-withdrawing group on the aryl ring (*para*-chloro, entry 5) gave an improved yield of 58%.[8] The retarding effect of sterics on the reaction are illustrated in entries 6−8 where ortho substituents on the aryl ring require higher reaction temperatures or give slightly reduced yields. As an illustration of the efficiency of this approach, a recent publication reported the synthesis of 3-(4-chlorophenyl)-1*H*-pyrrole (entry 5) in four steps and 48% overall yield.[5] The present approach proceeds in one step in 58% yield from commercially available starting materials.[9]

The synthesis of 3,4-diaryl pyrroles has not yet been reported using TOSMIC.[10] Therefore, we decided to investigate whether 1,2-diarylalkenes would also react under our conditions to give 3,4-diaryl pyrroles in a single step. The results are shown in Table 2.

Table 2. Synthesis of 3,4-Diaryl Pyrroles Using TOSMIC[a]

entry	substrate	product	T°C/ time	yield[b]
1			25°C/ 4h	91%
2			50°C/ 3h	55%
3			80°C/ 2h	49%
4			60°C/ 3h	53%
5			50°C/ 1h	72%

[a] TOSMIC (1.3 equiv), NaO*t*Bu (2 equiv), DMSO, *T* in °C. [b] Isolated yield after chromatography.

Again, electron-withdrawing aryl groups attached to the alkene led to higher yields of the desired pyrrole at lower temperatures and with shorter reaction times. Thus a bis-pyridyl-substituted alkene (entry 1) gave an excellent yield (91%) of the desired 3,4-dipyridyl pyrrole after only 4 h at

(7) Balasubramanian, T.; Strachan, J. P.; Boyle, P. D.; Lindsey, J. S *J. Org. Chem.* **2000**, *65*, 7919. For another example of saponification/decarboxylation route to 3-aryl pyrroles, see: Sakai, K.; Suzuki, N.; Kenichi, N.; Yoneda, N.; Onoda, Y.; Iwasawa, Y. *Chem. Pharm. Bull.* **1980**, *28*, 2384.

(8) Electron-rich arylalkenes such as 4-methoxystyrene gave low conversion upon extended reaction times at 100 °C.

(9) Further, 3-(phenyl)-1*H*-pyrrole (entry 1) was prepared previously in two steps and 32% overall yield: Boger, D. L.; Coleman, R. S.; Panek, J. S.; Yohannes, D. *J. Org. Chem.* **1984**, *49*, 4405.

(10) van Leusen has reported the synthesis of 3,4-diphenyl pyrrole using a *derivative* of TOSMIC: van Leusen, D.; van Echten, E.; van Leusen, A. M. *J. Org. Chem.* **1992**, *57*, 2245.

room temperature. When one of the pyridyl rings was changed to a phenyl (entry 2) or a thiophene ring (entry 3), good yields were still obtained but higher reaction temperatures were required. Entry 4 illustrates that alkyl-substituted alkenes will also undergo the reaction to give 3-aryl- and 4-alkyl-substituted pyrroles in good yields. Finally, the isoquinoline-substituted alkene (entry 5) further demonstrates that nonsymmetrical 3,4-disubstituted pyrroles can be assembled rapidly and in good yields. Again the utility of this approach is underlined as present methodology for the synthesis of nonsymmetrical 3,4-diaryl pyrroles is limited, requiring multiple synthetic steps.[11,12]

In summary, we have demonstrated that the synthesis of 3-aryl- and 3,4-diaryl-substituted pyrroles may be achieved *in a single step* from TOSMIC and commercially available or readily accessible aryl-substituted alkenes.[13,14] We believe this facile synthesis of aryl-substituted pyrroles represents a significant improvement over existing multistep sequences based on decarboxylation[5,7] or cross-coupling[6,12] sequences.

Acknowledgment. We thank Michael Gardner for help with determining HPLC yields.

Supporting Information Available: Reaction procedures and characterization of products (^{1}H and ^{13}C NMR, MS, and melting point). This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Ono, N.; Miyagawa, H.; Ueta, T.; Ogawa, T.; Tani, H. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1595.

(12) Liu, J. H.; Chan, H. W.; Wong, H. N. C. *J. Org. Chem.* **2000**, *65*, 3274.

(13) Kerins, F.; O'Shea, D. F. *J. Org. Chem.* **2002**, *67*, 4968−4971 and references cited within.

(14) Typical procedure: To a suspension of NaO*t*Bu (2 equiv) in dry DMSO was added a solution of the arylalkene (1 equiv) and tosylmethylisocyanate (1.3 equiv) in DMSO (0.1 M final concentration). The reaction mixture was stirred at the appropriate temperature for the required time, whereupon it was diluted with EtOAc and brine and shaken. The aqueous layer was washed with EtOAc (three times), dried over Na_2SO_4, filtered, concentrated, and purified by liquid chromatography on silica gel. For full experimental details and product characterization, please see Supporting Information.