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SYNTHESIS OF 2H-PYRROLO[3,4-C]QUINOLINE VIA AN ALDOL/VAN LEUSEN/STAUDINGER/AZA-WITTIG SEQUENCE

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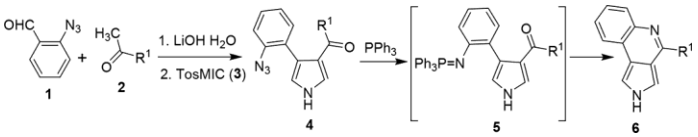
Abstract

An aldol/van Leusen/Staudinger/aza-Wittig reaction for the preparation of the derivatives of 2H-pyrrolo[3,4-c]quinolines from 2-azidobenzaldehyde, acetyl compounds and tosylmethyl isocyanide was developed. The process involves an aldol condensation of 2-azidobenzaldehyde with acetyl compound in base, and subsequently a van Leusen reaction to form the key pyrrole intermediates, then a Staudinger and intramolecular aza-Wittig reaction occurred with the addition of triphenylphosphine to complete the formation of pyrrolo[3,4-c]quinoline ring in high yields.

GRAPHICAL ABSTRACT



KEYWORDS: pyrrole, 2H-pyrrolo[3,4-c]quinolines, aldol/van Leusen/Staudinger/aza-Wittig reaction, 2-azidobenzaldehyde

INTRODUCTION

- Compounds possessing the pyrroloquinoline skeletons have exhibited widespread biological activities, such as antimalarial,[1,2] anticancer,[3,4] antiulcer,[5] and also have been found in many natural products.[6-8] Among these pyrroloquinoline derivatives, pyrrolo[3,4-c] quinolines attracted much attention due to their significant potential application to be used as analgesic[9] and caspase-3 inhibitor.[10-12] Particularly, a number of natural products also contain the core of pyrrolo[3,4-c]quinoline ring,[13-15] and some of them have exhibited excellent antitumor activities and selectivity.[16] Some literatures reported the methods for the synthesis of pyrrolo[3,4-c]quinoline derivatives by using van Leusen/hydrogenation/ condensation reaction,[9,17-19] electrocyclisation reaction[20,21] or Pfitzinger/dehydration reaction,[3,10-12,22] However, a simple and efficient way to construct this skeleton is still in need.

- Over the past twenty years, the isocyanide based multicomponent reactions (IMCRs) have become a superior tool in the synthesis of combinational libraries of compounds.[23-25] Van Leusen reaction is an isocyanide based reaction and well-known in the construct of heterocycles, such as oxazoles,[26] pyrroles[27] and imidazoles.[28] On the other hand, the strategy of tandem Staudinger/aza-Wittig-mediated annulation has been widely used in the synthesis of heterocyclic compounds.[29] Moreover, the synthesis of molecules with carbon-nitrogen double bonds by using the aza-Wittig reactions together with post transformation has received extensive attention.[30-31] Therefore it is anticipated that combining the isocyanide based reaction with a post aza-Wittig reaction would facilitate access to a series of biologically useful fused heterocycles.[32-35] Recently, we have synthesized a series of benzoxazines,[36] dihydroquazolines,[37] indolo[1,2-c]quinazolines[38] and indoles[39] in our laboratory using isocyanide as starting material. Hence, continuing our interest in the construct of various heterocycles via aza-Wittig reaction,[40-44] we wish to report herein a simple and efficient synthesis of 2H-pyrrolo[3,4-c]quinoline derivatives, which were prepared via sequential aldol/van Leusen/Staudinger/aza-Wittig reaction in high yields.

RESULTS AND DISCUSSION

The initial investigation for the construction of 3,4-disubstituted pyrrole derivative focused on the one pot model reaction between 2-azidobenzaldehyde (**1**), 4-methoxyacetophenone (**2a**) and tosylmethyl isocyanide (TosMIC **3**). When 1.5 equiv of lithium hydroxide monohydrate was added to the mixture of 2-azidobenzaldehyde, and

4-methoxyacetophenone in ethanol, the aldol condensation reaction was carried out smoothly and completed within 40 min which was monitored by TLC. And then one equiv of TosMIC was added to the mixture without the isolation of the aldol reaction product. And the van Leusen reaction was completed with the end of the solid precipitated from the ethanol (Scheme 1). The substrate scope of the acetyl compounds was evaluated and the results are listed in Table 1 (Entries 1-10). The pyrrole derivatives were obtained all in moderate to high yields whether the acetyl compounds that used were alkyl or aryl.

The followed Staudinger and intramolecular aza-Wittig reaction of azides **4** with triphenylphosphine was examined. When azides **4** were treated with one equiv of triphenylphosphine in dichloromethane at ambient temperature, the expected Staudinger reaction and intramolecular aza-Wittig reaction occurred with a reasonable time at room temperature and 2H-pyrrolo[3,4-c]quinoline derivatives were isolated in good yields (85-95%, Scheme 2, Table 2, **6a**-**6j**). The formation of 2H-pyrrolo[3,4-c]quinoline derivatives can be viewed as an initial Staudinger reaction between the azide **4** and triphenylphosphine to form the key intermediate iminophosphorane **5**. The 2H-pyrrolo[3,4-c]quinolines **6** were finally produced via the further intramolecular aza-Wittig reaction of **5** directly with the elimination of triphenylphosphine oxide.

The compounds of 2H-pyrrolo[3,4-c]quinoline derivatives **6** were confirmed by their spectral data. For example, the ^{1}H NMR spectrum of **6a** showed singlet at 3.86 ppm due to the methoxyl group linking to the phenyl ring. And the signals attributable to the

protons of the pyrrolo[3,4-c]quinoline and phenyl rings were found at 8.19-7.13 ppm as mutiplets, while the signal of the pyrrole ring belong to the nitrogen-hydrogen bond was found at 12.84 ppm as singlet compared to singlet at 11.74 ppm in the intermediate pyrrole ring **4a**. The ^{13}C NMR spectrum data in **6a** showed the carbon signal of carbon-nitrogen double bond at 160.2 ppm and in the intermediate **4a** the carbon signal of carbonyl group at 189.0 ppm.

CONCLUSIONS

In conclusion, we have developed an efficient synthesis of 2H-pyrrolo[3,4-c]quinoline derivatives via combining aldol/van Leusen/Staudinger/aza-Wittig reactions starting from 2-azidobenzaldehyde, acetyl compounds and TosMIC in high yields. Due to the mild reaction conditions, easily accessible starting material and straightforward product isolation, We think that the versatile synthetic approach discussed here in many cases compares favorably with other existing methods for synthesis of many biologically active pyrrolo[3,4-c]quinoline derivatives, and further application, optimization and in natural product synthesis of the method are underway.

EXPERIMENTAL SECTION

General Methods.

Reactions were generally carried out in an appropriate round bottom flask with magnetic stirring. Thin layer chromatography (TLC) was performed on a silica gel. All melting points were determined using a X-4 model apparatus and were uncorrected. IR were recorded on a PE-983 infrared spectrometer as KBr pellets with absorption in cm^{-1}. NMR

spectra were recorded on Bruker Avance III 400 spectrometer in $CDCl_3$ or DMSO-d_6. Mass spectra were obtained on a LC-MS-2010A spectrometer with ESI. Elementary analyses were taken on a Vario EL III elementary analysis instrument.

General Preparation of 3,4-Disubstituted Pyrroles (4a-4j).

Lithium hydroxide monohydrate (0.18 g, 4.5 mmol) was added to the mixture of 2-azidobenzaldehyde **1** (0.44 g, 3 mmol) and acetyl compounds **2** (3 mmol) in ethanol, the aldol condensation reaction was carried out smoothly and completed within 40 min which was monitored by TLC. And then TosMIC (0.59 g, 3 mmol) was added to the mixture without the isolation of the aldol reaction product. And the van Leusen reaction was completed with the end of the solid precipitated from the ethanol, then filtered and washed with ethanol. The residual was recrystallized from methylene dichloride/ethanol to give **4a-4j** in good yields.

(4-(2-Azidophenyl)-1H-Pyrrol-3-yl)(4-Methoxyphenyl)Methanone (4a)

Yellow crystals, mp 168-169 ºC; IR: 3176, 2119, 1601, 1508, 1288, 895, 761; ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm): 11.74 (s, 1H, NH), 7.36 (d, 2H, J = 8.0 Hz, Ar-H), 7.25 (q, 3H, J = 8.0 Hz, Ar-H), 7.13-7.09 (m, 3H, Ar-H), 6.96 (q, 2H, J = 2.8 Hz, Ar-H), 3.80 (s, 3H, OCH_3); ^{13}C NMR (DMSO-d_6, 100 MHz) δ (ppm): 189.0, 151.7, 136.8, 131.2, 128.2, 127.6, 124.7, 124.4, 123.1, 122.3, 120.6, 119.9, 118.8, 111.5, 110.4, 55.6; LC-MS (m/z): 318; Anal. Calcd for $C_{18}H_{14}N_4O_2$: C, 67.92; H, 4.43; N, 17.60; Found: C, 67.91; H, 4.49; N, 17.81;

General Preparation of 2H-Pyrrolo[3,4-c]Quinolines (6a-6j).

To a stirred solution of 3,4-disubstituted pyrroles **4** (1 mmol) in dichloromethane (5 mL) was added drop wise of triphenylphosphine (0.26 g, 1 mmol) in dichloromethane (5 mL) at room temperature. The reaction mixture was stirred for 3-6 hours at room temperature and monitored by thin-layer chromatography. Once completed, the solvent was removed off under reduced pressure and the residual was recrystallized from dichloromethane/ petroleum ether to give 2H-pyrrolo[3,4-c]quinolines **6**.

4-(4-Methoxyphenyl)-2H-Pyrrolo[3,4-c]Quinoline (6a)

White crystals, mp 177-178 ºC (lit.[17] mp: 168-170 ºC); IR: 3431, 2962, 1617, 1498, 1444, 1250, 1031, 946, 831, 761, 740; ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm): 12.84 (s, 1H, NH), 8.19-8.17 (m, 3H, Ar-H), 8.10-7.90 (m, 2H, Ar-H), 7.72 (s, 1H, Ar-H), 7.64-7.43 (m, 2H, Ar-H), 7.13 (t, 2H, J = 9.6 Hz, Ar-H), 3.86 (s, 3H, OCH_3); ^{13}C NMR (DMSO-d_6, 100 MHz) δ (ppm): 160.2, 154.7, 142.3, 132.5, 129.8, 129.0, 128.3, 125.7, 124.5, 122.6, 121.6, 115.9, 114.2, 113.9, 110.1, 55.2; LC-MS (m/z): 274; Anal. Calcd for $C_{18}H_{14}N_2O$: C, 78.81; H, 5.14; N, 10.21; Found: C, 78.87; H, 5.11; N, 10.10;

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SUPPORTING INFORMATION

Full experimental detail, IR, CHN analysis, mass spectra, and ^{1}H NMR and ^{13}C NMR spectra for this article can be accessed on the publisher's website.

REFERENCES

1. Okanya, P. W.; Mohr, K. I.; Gerth, K.; Jansen, R.; Müller, R. *J. Med. Chem.* **2011**, *74*, 603-608.

2. Carroll, A. R.; Duffy, S.; Avery, V. M. *J. Org. Chem.* **2010**, *75*, 8291-8294.

3. Ganjian, I.; Khorshidi, M.; Lalezari, I. *J. Heterocyclic Chem.* **1991**, *28*, 1173-1175.

4. Gasparotto, V.; Castagliuolo, I.; Chiarelotto, G.; Pezzi, V.; Montanaro, D.; Brun, P.; Palù, G.; Viola, G.; Ferlin, M. G. *J. Med. Chem.* **2006**, *49*, 1910-1915.

5. Brown, T. H.; Ife, R. J.; Keeling, D. J.; Laing, S. M.; Leach, C. A.; Parsons, M. E.; Price, C. A.; Reavill, D. R.; Wiggall, K. J. *J. Med. Chem.* **1990**, *33*, 527-533.

6. Sangnoi, Y.; Sakulkeo, O.; Yuenyongsawad, S.; Kanjana-opas, A.; Ingkaninan, K.; Plubrukarn, A.; Suwanborirux, K. *Mar. Drugs* **2008**, *6*, 578-586.

7. Liu, G. S.; Dong, Q. L.; Yao, Y. S.; Yao, Z. J. *Org. Lett.* **2008**, *10*, 5393-5396.

8. Osborne, D.; Stevenson, P. J. *Tetrahedron Lett.* **2002**, *43*, 5469-5470.

9. Furlotti, G.; Alisi, M. A.; Apicella, C.; Capezzone de Joannon, A.; Cazzolla, N.; Costi, R.; Cuzzucoli Crucitti, G.; Garrone, B.; Iacovo, A.; Magarò, G.; Mangano, G.; Miele, G.; Ombrato, R.; Pescatori, L.; Polenzani, L.; Rosi, F.; Vitiello, M.; Di Santo, R. *J. Med. Chem.***2012**, *55*, 9446-9466.

10. Kravchenko, D. V.; Kysil, V. M.; Tkachenko, S. E.; Maliarchouk, S.; Okun, I. M.; Ivachtchenko, A. V. *Il Farmaco* **2005**, *60*, 804-809.

11. Kravchenko, D. V.; Kuzovkova, Y. A.; Kysil, V. M.; Tkachenko, S. E.; Maliarchouk, S.; Okun, I. M.; Balakin, K. V.; Ivachtchenko, A. V. *J. Med. Chem.* **2005**, *48*, 3680-3683.

12. Kravchenko, D. V.; Kysil, V. V.; Ilyn, A. P.; Tkachenko, S. E.; Maliarchouk, S.; Okun, I. M.; Ivachtchenko, A. V. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1841-1845.

13. Inman, W. D.; O'Neill-Johnson, M.; Crews, P. *J. Am. Chem. Soc.* **1990**, *112*, 1-4.

14. Smith, C. J.; Venables, D. A.; Hopmann, C.; Salomon, C. E.; Jompa, J.; Tahir, A.; Faulkner, D. J.; Ireland, C. M. *J. Nat. Prod.* **1997**, *60*, 1048-1050.

15. Ford, P. W.; Davidson, B. S. *J. Nat. Prod.* **1997**, *60*, 1051-1053.

16. Ralifo, P.; Sanchez, L.; Gassner, N. C.; Tenney, K.; Lokey, R. S.; Holman, T. R.; Valeriote, F. A.; Crews, P. *J. Nat. Prod.* **2007**, *70*, 95-99.

17. Lu, X. M.; Li, J.; Cai, Z. J.; Wang, R.; Wang, S. Y.; Ji, S. J. *Org. Biomol. Chem.* **2014**, *12*, 9471-9477.

18. Wang, R.; Xu, X. P.; Meng, H.; Wang, S. Y.; Ji, S. J. *Tetrahedron* **2013**, *69*, 1761-1766.

19. Santo, R. D.; Costi, R.; Forte, M.; Galeffi, C. *Arkivoc* **2004**, *v*, 181-195.

20. Pintér, Á.; Nyerges, M.; Virányi, A.; Tőke, L. *Tetrahedron Lett.* **2003**, *44*, 2343-2346.

21. Nyerges, M.; Pintér, Á.; Virányi, A.; Blaskó, G.; Tőke, L. *Tetrahedron* **2005**, *61*, 8199-8205.

22. Ivachtchenko, A. V.; Kobak, V. V.; Il'yin, A. P.; Trifilenkov, A. S.; Busel, A. A. *J. Comb. Chem.* **2003**, *5*, 645-652.

23. Domling, A. *Chem. Rev.* **2006**, *106*, 17-89.

24. Niu, T. F.; Lu, G. P.; Cai, C. *J. Chem. Res.* **2011**, 444-447.

25. Dömling, A.; Ugi, I. *Angew. Chem. Int. Ed.* **2000**, *39*, 3168-3210.

26. Wu, B.; Wen, J.; Zhang, J.; Li, J.; Xiang, Y. Z.; Yu, X. Q. *Synlett* **2009**, *2009*, 500-504.

27. Artico, M.; Di Santo, R.; Costi, R.; Massa, S.; Retico, A.; Artico, M.; Apuzzo, G.; Simonetti, G.; Strippoli, V. *J. Med. Chem.* **1995**, *38*, 4223-4233.

28. Van Leusen, A. M.; Wildeman, J.; Oldenziel, O. H. *J. Org. Chem.* **1977**, *42*, 1153-1159.

29. Palacios, F.; Alonso, C.; Aparicio, D.; Rubiales, G.; de los Santos, J. M. *Tetrahedron* **2007**, *63*, 523-575.

30. Funicello, M.; Laboragine, V.; Pandolfo, R.; Spagnolo, P. *Synlett* **2010**, 77-80.

31. Nie, Y.-B.; Wang, L.; Ding, M. W. *J. Org. Chem.* **2012**, *77*, 696-700.

32. Wang, L.; Ren, Z. L.; Chen, M.; Ding, M.-W. *Synlett* **2014**, *25*, 721-723.

33. Ramazani, A.; Rezaei, A. *Org. Lett.***2010**, *12*, 2852-2855.

34. Corres, N.; Delgado, J. J.; Garcia-Valverde, M.; Marcaccini, S.; Rodriguez, T.; Rojo, J.; Torroba, T. *Tetrahedron* **2008**, *64*, 2225-2232.

35. Sanudo, M.; Garcia-Valverde, M.; Marcaccini, S.; Delgado, J. J.; Rojo, J.; Torroba, T. *J. Org. Chem.* **2009**, *74*, 2189-2192.

36. He, P.; Wu, J.; Nie, Y. B.; Ding, M. W. *Tetrahedron* **2009**, *65*, 8563-8570.

37. He, P.; Wu, J.; Nie, Y. B.; Ding, M. W. *Eur. J. Org. Chem.* **2010**, 1088-1095.

38. He, P.; Nie, Y. B.; Wu, J.; Ding, M. W. *Org. Biomol. Chem.* **2011**, *9*, 1429-1436.

39. He, P.; Ding, M. W. *Chinese J. Struct. Chem.* **2013**, *32*, 306-310.

40. He, P.; Li, Z. F.; Hou, Q. F.; Wang, Y. L.; Zhao, K. *Arkivoc* **2013**, 199-209.

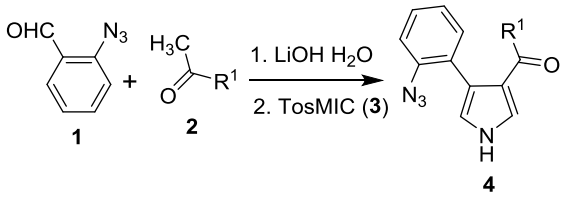
41. Hu, Y. G.; Li, L.; Zhang, Q. Y.; Zhang, A. N.; Feng, C.; He, P. *Heterocycl. Commun.* **2015**; 21, 345-348.

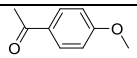
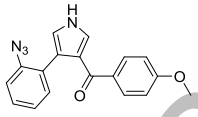
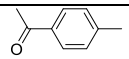
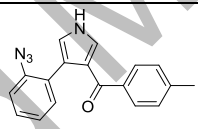
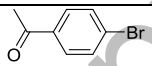
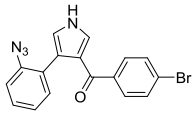
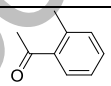
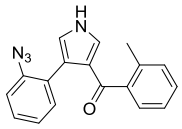
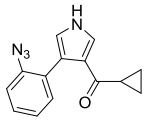
42. Wei, J.; Nie, B. J.; Peng, R.; Cheng, X. H.; Wang, S.; He, P. *Synlett* **2016**, *27*, 626-630.

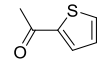
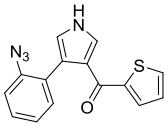
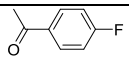
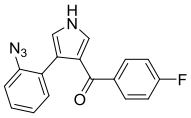
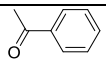
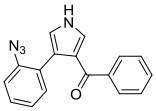
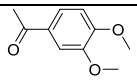
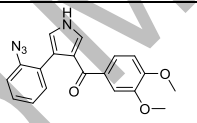
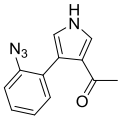
43. Qu, F.; He, P.; Hu, R. F.; Cheng, X. H.; Wang, S.; Wu, J. *Synth. Commun.* **2015**, *45*, 2802-2809.

44. Qu, F.; Hu, R. F.; Gao, L.; Wu, J.; Cheng, X. H.; Wang, S.; He, P. *Synthesis* **2015**, *47*, 3701-3710.

Table 1. Synthesis of pyrroles **4** form 2-azidobenzaldehyde **1**, acetyl compounds **2** and TosMIC **3**

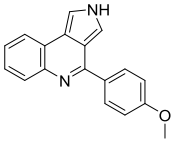
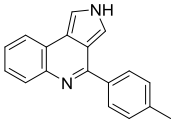
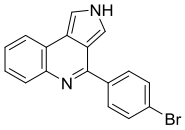
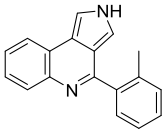
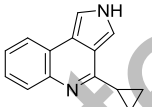
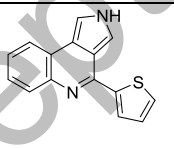
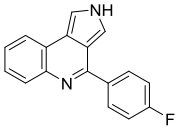
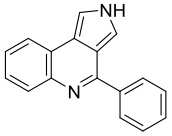


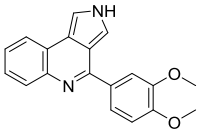
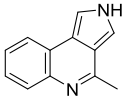
Entry	Acetyl compound	Product		Conditions	Yield (%)[a]
1	**2a** 	**4a**		First 40 min at 0°C Then 120 min at 25°C	88
2	**2b** 	**4b**		First 40 min at 0°C Then 120 min at 25°C	90
3	**2c** 	**4c**		First 40 min at 0°C Then 120 min at 25°C	82
4	**2d** 	**4d**		First 40 min at 0°C Then 120 min at 25°C	88
5	**2e** 	**4e**		First 40 min at 20°C Then 120 min	80

				at 25°C	
6	**2f** 	**4f** 		First 40 min at 0°C Then 180 min at 25°C	88
7	**2g** 	**4g** 		First 40 min at 0°C Then 120 min at 25°C	90
8	**2h** 	**4h** 		First 40 min at 0°C Then 120 min at 25°C	85
9	**2i** 	**4i** 		First 40 min at 0°C Then 120 min at 25°C	95
10	**2j** 	**4j** 		First 40 min at 20°C Then 120 min at 25°C	82

[a]Isolated yields based on 2-azidobenzaldehyde **1**.

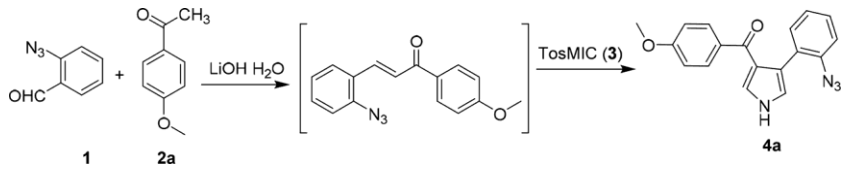
Table 2. Preparation of 2H-pyrrolo[3,4-c]quinolines **6** via Staudinger/aza-Wittig reaction from azides **4**

Entry	Product		Conditions	Yield (%)[a]
1	**6a**		3 hours 25°C	90
2	**6b**		3 hours 25°C	92
3	**6c**		3 hours 25°C	88
4	**6d**		3 hours 25°C	96
5	**6e**		6 hours 25°C	90
6	**6f**		4 hours 25°C	88
7	**6g**		3 hours 25°C	92
8	**6h**		3 hours 25°C	95

9	**6i**		3 hours 25°C	92
10	**6j**		6 hours 25°C	85

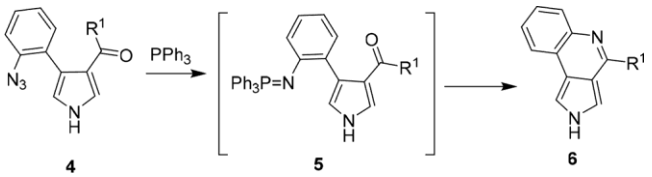
[a]Isolated yields based on azides **4**.

Scheme 1. Synthesis of 3,4-disubstituted pyrrole **4a.**



1 2a 4a

Scheme 2. Preparation of 2H-pyrrolo[3,4-c]quinolines **6** via Staudinger/aza-Wittig reaction.



4 5 6