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An efficient one-pot reaction of indoles, nitroacetate, and paraformaldehyde for the synthesis of tryptophan derivatives

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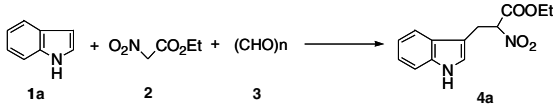
Abstract—An efficient method for the synthesis of tryptophan analogues has been developed via one-pot reaction of commercial available indoles, ethyl nitroacetate, and paraformaldehyde in the presence of molecular sieves. The reaction provided tryptophan nitro-precursors in moderate to good yields, which were further converted to α-hydroxymethylated tryptophan derivatives catalyzed by DABCO in high yields.

As an essential amino acid, tryptophan along with its analogues has attracted much attention in the area of pharmaceutical and biochemical research. α-Tryptophan was reported to inhibit the growth of *Bacterium coli*[1] and to be used as IDO inhibitors.[2] In addition, tryptophan analogues are important building blocks for the synthesis of biologically active compounds ranging from peptide mimetics to natural products.[3] Among various synthetic methods, two strategies have been used for the preparation of tryptophan analogues. One is based on indole chemistry[4] and another involves the construction of indole ring by Fischer-indole cyclization or palladium catalyzed heteroannulation.[5] However, most methods either need pre-synthesized substrates or require multi-step synthetic reactions.

Nowadays, one-pot multicomponent reactions have emerged as valuable tools in organic synthesis for reducing operative steps and enhancing synthesis efficiency.[6] In 1978, Yonemitsu reported a one-pot reaction of indoles, Meldrum's acid, and aldehydes to synthesize indolepropionates[7] that was developed to tryptophan derivatives by Laronze via further multistep chemical transformation of alcoholysis, domino acylazide formation-Curtius rearrangment-benzylalcohol solvolysis and deprotection.[8] Such synthetic methodology provided an approach to β-substituted tryptophan derivatives. However, in case of simple tryptophan derivatives without substituents in β-position, base-catalyzed one-pot reaction of indoles, Meldrum's acid and formaldehyde afforded a mixture of condensation products and further hydroxymethylated derivatives.[9] On the other hand, nitroacetate, a widely used reactive methylene compound,[10] has been rarely reported in Yonemitsu reaction, probably due to the highly reactive intermediates generated in condensation with formaldehyde, which is easily polymerized under heating and basic conditions. Herein, we wish to report an efficient one-pot reaction of indoles, nitroacetate, and paraformaldehyde to provide tryptophan precursors in the presence of molecular sieves. Tryptophan derivatives are obtained in high yields upon reduction of nitro group to amino group.

In the preliminary study, 37% aqueous formaldehyde solution was used in the one-pot reaction (Scheme 1). In the presence of HOAc as a promoter, the reaction of indole (**1a**), ethyl nitroacetate (**2**), and aqueous formaldehyde (**3**) provided tryptophan nitro-precursor **4a** in



Scheme 1.

Keywords: Tryptophan; One-pot; Indole; Nitroacetate.
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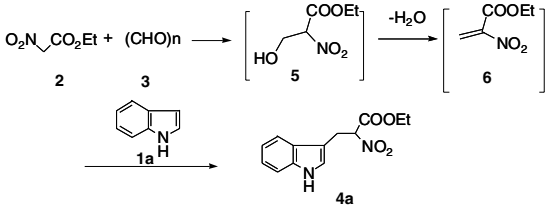
Table 1. One-pot reaction of indole **1a**, nitroacetate **2**, and paraformaldehyde **3**[a]

Entry	Ratio (**1a**:**2**:**3**)	Solvent	Additive	Yield[c] (%)
1[b]	3:1:3	THF	HOAc	27
2	3:1:3	THF	4AMS	40
3	3:1:3	Toluene	4AMS	62
4[d]	3:1:3	Toluene	4AMS	50
5	1:4:8	Toluene	4AMS	92
6	1:4:8	Toluene	4AMS/$Cu(OTf)_2$[e]	38
7	1:4:8	CH_3CN	4AMS	35
8	1:4:8	Toluene	—	14

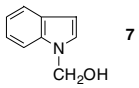
[a] 4 Å MS: 500 mg per 1 mmol ethyl nitroacetate, 70 °C, 7 h.
[b] 37% aqueous formaldehyde solution, 3 equiv HOAc.
[c] Isolated yield.
[d] Reflux.
[e] 5 mol % $Cu(OTf)_2$.

only 27% yield (Table 1, entry 1). Since synthesis of compound **4a** by such one-pot reaction could be considered as sequential reactions of nitroaldol condensation and Michael addition and a molecule of water would be generated (Scheme 2),[11] we used paraformaldehyde instead of aqueous formaldehyde solution, in which molecular sieves were employed to absorb the water. As expected, one-pot reaction of indole (**1a**), ethyl nitroacetate (**2**), and paraformaldehyde in the presence of molecular sieves afforded **4a** in 62% yield in toluene (entry 3). Solvent played a key role in the reaction. The one-pot condensation proceeded in toluene better than in THF or in CH_3CN (entries 3 and 4). High temperature (in reflux toluene) resulted in low yield (entries 4 vs 3).

It was important to note that in the absence of molecular sieves,[12] the yield dropped dramatically (entries 8 vs 5). *A stepwise one-pot reaction* which ethyl nitroacetate (**2**) reacted with paraformaldehyde (**3**) first in the presence of molecular sieves, then added indole resulted in only 61% yield of **4a** and remained indole was recovered. Therefore, indole reacted with in situ generated **6** is very important in order to obtain high yield. When a Lewis acid $Cu(OTf)_2$ was added in the reaction system, the yield was decreased dramatically (entry 6). It should be noted that the side reaction of indole with paraformaldehyde (**3**) was entirely inhibited under the reaction conditions, even though excess paraformaldehyde was used (entry 5). The control experiment showed that the reaction of indole with paraformaldehyde provided only *N*-alkylated product **7** in 34% yield. The best ratio of indole, ethyl nitroacetate, and paraformaldehyde was found to be 1:4:8 and toluene was the best solvent (entry 5).



Scheme 2.



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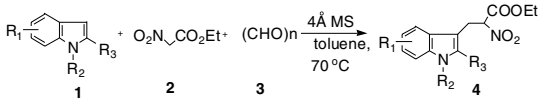
Under the optimized conditions, various indole derivatives **1** could react with ethyl nitroacetate **2** and paraformaldehyde **3** in one-pot (Table 2). In all cases, tryptophan nitro-precursors **4** were obtained in moderate to good yields. When indoles have electron-donating substituents, the reaction provided **4a**–**i** in excellent yields, but the electron-withdraw group resulted in low yield (entry 6).

Tryptophan precursors **4** could be easily transformed to the corresponding tryptophan analogues by reduction of nitro group. As an application of the present one-pot reaction, β-carboline **8** was synthesized from **4**. Treatment of **4a** with Zn/H^{+}[13] followed by Pictet–Spengler reaction using EtCHO in the presence of TFA provided ethyl 1-ethyl-2,3,4,9-tetrahydro-1*H*-β-carboline-3-carboxylate **8** in 65% overall yield and 7:3 ratio of cis/trans diastereomers (Scheme 3).

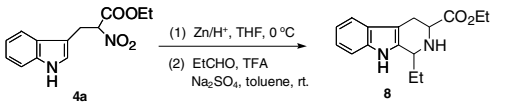
In the one-pot condensation of indole **1c**, ethyl nitroacetate (**2**), and paraformaldehyde (**3**), trace amount of hydroxymethylated product **9c** was observed by a fur-

Table 2. One-pot reactions of indoles **1**, ethyl nitroacetate **2**, and paraformaldehyde **3** for the synthesis of tryptophan precursors **4**[a]



Entry	Indole **1**	Time (h)	Product **4**	Yield[b] (%)
1	**1a**	7	**4a**	92
2	**1b**	6	**4b**	94
3	**1c**	6	**4c**	95
4	**1d**	6	**4d**	96
5	**1e**	10	**4e**	73
6	**1f**	12	**4f**	44
7	**1g**	10	**4g**	88
8	**1h**	7	**4h**	91
9	**1i**	6	**4i**	91

[a] Reaction temperature: 70 °C, **1**:**2**:**3** = 1:4:8.
[b] Isolated yield.

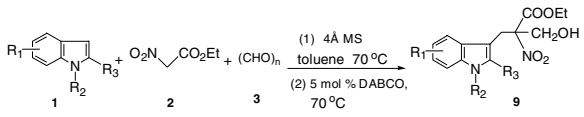


Scheme 3.

ther aldol reaction. Since α-substituted tryptophans showed interesting biological properties,[14] we transformed tryptophan precursors **4** to corresponding hydroxymethylated derivatives **9** under basic conditions. Table 3 showed the one-pot reaction for the synthesis of α-hydroxymethylated tryptophan precursors **9**. After three component condensation of indoles, nitroacetate, and paraformaldehyde, 5 mol % DABCO was added to generate the hydroxymethylated derivatives **9** in good yields (Table 3).[15]

In conclusion, an efficient method for the synthesis tryptophan analogues or its α-hydroxymethylated derivatives has been developed via one-pot reaction of commercial available indole, ethyl nitroacetate, and paraformaldehyde. In the presence of molecular sieves, the reaction provided tryptophan nitro-precursors in moderate to good yields. A further reaction catalyzed by DABCO affords α-hydroxymethylated tryptophan precursors in good yields.

Table 3. One-pot reactions of indoles **1**, ethyl nitroacetate **2**, and paraformaldehyde **3** for the synthesis of hydroxymethylated tryptophan precursors **9**[a]



Entry	Indole **1**	Product **9**	Yield[b] (%)
1	**1a**	**9a**	91
2	**1b**	**9b**	92
3	**1c**	**9c**	90
4	**1d**	**9d**	78
5	**1e**	**9e**	72
6	**1f**	**9f**	40
7	**1g**	**9g**	70
8	**1h**	**9h**	89
9	**1i**	**9i**	90

[a] **1**:**2**:**3** = 1:4:8, 70 °C, 10 h; then 5 mol % DABCO, 3 equiv paraformaldehyde, 70 °C, 6 h.

[b] Isolated yield.

Acknowledgments

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References and notes

1. Anderson, M. *Science* **1945**, *101*, 565.
2. (a) Van Essevldt, B. C.; Van Delft, F. L.; Smits, J. M.; De Gelder, R.; Schoemaker, H. E.; Rutjes, F. P. *Adv. Synth. Catal.* **2004**, *346*, 823; (b) Peterson, A. G.; Migawa, M. T.; Martin, M. J.; Hamaker, L. K.; Czerwinski, K. M.; Zhang, W.; Arend, R. A.; Fiestte, P. L.; Ozaki, Y.; Will, J. A.; Brown, R. R.; Cook, J. M. *Med. Chem. Res.* **1994**, *3*, 531.
3. For examples: (a) Reddy, R.; Jaquith, J. B.; Neelagiri, V. R.; Saleh-Hanna, S.; Durst, T. *Org. Lett.* **2002**, *4*, 695; (b) Wen, S. J.; Yao, Z. J. *Org. Lett.* **2004**, *6*, 2721; (c) Miyake, F. Y.; Yakushijin, K.; Horne, D. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 5357; (d) Feldman, K. S.; Karatjas, A. G. *Org. Lett.* **2004**, *6*, 2849; (e) Gonzalez-Vera, J. A.; Garcia-Lopez, M. T.; Herranz, R. *Org. Lett.* **2004**, *6*, 2641.
4. Selective examples: (a) Bartoli, G.; Bosco, M.; Giuli, S.; Giuliani, A.; Lucarelli, L.; Marcantoni, E.; Sambri, L.; Torregiani, E. J. *Org. Chem.* **2005**, *70*, 1941; (b) Jiang, Y. W.; Ma, D. W. *Tetrahedron Lett.* **2002**, *43*, 7013; (c) Wang, W.; Xiong, C. Y.; Yang, J. Q.; Hruby, V. J. *Tetrahedron Lett.* **2001**, *42*, 7717; (d) Carlier, P. R.; Lam, P. C.; Wong, D. M. *J. Org. Chem.* **2002**, *67*, 6256; (e) Vedejs, E.; Kongkittingam, C. *J. Org. Chem.* **2001**, *66*, 7355; (f) Meseguer, B.; Alonso-Díaz, D.; Griebenow, N.; Herget, T.; Waldmann, H. *Chem. Eur. J.* **2000**, *6*, 3943; (g) Nemes, C.; Jeannin, L.; Sapi, J.; Laronze, M.; Seghir, H.; Augé, F.; Laronze, J.-Y. *Tetrahedron* **2000**, *56*, 5479; (h) Hurt, C. R.; Lin, R.-H.; Rapoport, H. *J. Org. Chem.* **1999**, *64*, 225.
5. (a) Gorohovsky, S.; Meir, S.; Shkoulev, V.; Byk, G.; Gellerman, G. *Synlett* **2003**, 1411; (b) Liu, R. Y.; Zhang, P. W.; Gan, T.; Cook, J. M. *J. Org. Chem.* **1997**, *62*, 7447; (c) Jia, Y. X.; Zhu, J. P. *Synlett* **2005**, 2469; (d) Li, X. Y.; Yin, W. Y.; Sarma, P. V. V. S.; Zhou, H.; Ma, J.; Cook, J. M. *Tetrahedron Lett.* **2004**, *45*, 8569; (e) Ma, C. R.; Liu, X. X.; Li, X. Y.; Flippen-Anderson, J.; Yu, S.; Cook, J. M. *J. Org. Chem.* **2001**, *66*, 4525.
6. Zhu, J. P.; Bienaymé, H. *Multicomponent Reactions*; Wiley-VCH: Weinheim, 2005.
7. (a) Oikawa, Y.; Hirasawa, H.; Yonemitsu, O. *Tetrahedron Lett.* **1978**, 1759; (b) Oikawa, Y.; Hirasawa, H.; Yonemitsu, O. *Chem. Pharm. Bull.* **1982**, *30*, 7437.
8. (a) Jeannin, L.; Nagy, T.; Vassileva, E.; Sapi, J.; Laronze, J. Y. *Tetrahedron Lett.* **1995**, *36*, 2057; (b) Nemes, C.; Jeannin, L.; Sapi, J.; Laronze, M.; Seghir, H.; Augé, F.; Laronze, J. Y. *Tetrahedron* **2000**, *56*, 5479; (c) Dardennes, E.; Kovács-Kulyassa, Á.; Boisbrum, M.; Petermann, C.; Laronze, J. Y.; Sapi, J. *Tetrahedron: Asymmetry* **2005**, *16*, 1329.
9. (a) Nemes, C.; Laronze, J.-Y. *Synthesis* **1999**, 254; (b) Sapi, J.; Laronze, J. Y. *ARKIVOC* **2004**, *7*, 208.

10. Selected nitroacetate application in the synthesis of nonnatural amino acids: (a) Fornicola, R.; Montgomery, J. *Tetrahedron Lett.* **1999**, *40*, 8337; (b) Fu, Y. W.; Hammarstrom, L. G. J.; Miller, T. J.; Fronczek, F. R.; McLaughlin, M. L.; Hammer, R. P. *J. Org. Chem.* **2001**, *66*, 7118; (c) Kislyi, V. V.; Samet, A. V.; Semenov, V. V. *Curr. Org. Chem.* **2001**, *5*, 553; (d) Fornicola, R. S.; Oblinger, E.; Montgomery, J. *J. Org. Chem.* **1998**, *63*, 3528; (e) Rosini, G.; Ballini, R. *Synthesis* **1988**, 833.
11. Ballini, R.; Clemente, R. R.; Palmieri, A.; Petrini, M. *Adv. Synth. Catal.* **2006**, *348*, 191.
12. (a) Matsuura, T.; Bode, J. W.; Hachisu, Y.; Suzuki, K. *Synlett* **2003**, 1746; (b) Adinolfi, M.; Barone, G.; Iadonisi, A.; Schiattarella, M. *Org. Lett.* **2003**, *5*, 987; (c) Antonioletti, R.; Bonadies, F.; Locati, L.; Scettri, A. *Tetrahedron Lett.* **1992**, *33*, 3205; (d) Mizuno, M.; Kobayashi, K.; Nakajima, H.; Koya, M.; Inazu, T. *Synth. Commun.* **2002**, *32*, 1665; (e) Breck, D. W. *Zeolite Molecular Sieves*; John Wiley & Sons: New York, 1974.
13. Barroca, N.; Schmidt, R. R. *Org. Lett.* **2004**, *6*, 1551.
14. (a) Ashwood, V. A.; Field, M. J.; Horwell, D. C.; Julien-Larose, C.; Lewthwaite, R. A.; McCleary, S.; Pritchard, M. C.; Raphy, J.; Singh, L. *J. Med. Chem.* **2001**, *44*, 2276; (b) Zembower, D. E.; Gilbert, J. A.; Ames, M. M. *J. Med. Chem.* **1993**, *36*, 305.
15. *Typical procedure for one-pot reaction: Paraformaldehyde* **3** (72 mg, 2.4 mmol) and 4 Å MS (600 mg) were added to a solution of indole **1a** (35 mg, 0.3 mmol) and ethyl nitroacetate **2** (133 μL, 1.2 mmol) in 1.5 mL toluene placed in a 10 mL tube. The reaction mixture was stirred at 70 °C for 7 h and then cooled to room temperature. The mixture was filtered through a pad of Celite and washed with EtOAc (15 mL). The filtrate was concentrated under reduced pressure, and the residue was purified by flash chromatography on silica gel to provide ethyl 3-(1*H*-indol-3-yl)-2-nitropropanoate (**4a**, 72 mg, 92%). *Ethyl 3-(5-bromo-1H-indol-3-yl)-2-nitropropanoate* (**4g**): brown oil. FTIR(neat): 3429, 2984, 1746, 1562, 1462, 1373, 1270, 1211, 1098, 1019, 859, 797 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 8.15$ (br s, 1H), 7.70 (d, $J = 1.8$ Hz, 1H), 7.32–7.22 (m, 2H), 7.07 (d, $J = 2.5$ Hz, 1H), 5.39 (dd, $J = 5.5$, 9.5 Hz, 1H), 4.29 (q, $J = 7.1$ Hz, 2H), 3.69 (dd, $J = 9.5$, 15.0 Hz, 1H), 3.60 (dd, $J = 5.5$, 15.0 Hz, 1H), 1.29 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 164.2$, 134.7, 128.3, 125.5, 124.7, 120.7, 113.4, 112.9, 108.1, 88.3, 63.2, 26.4, 13.9. HRMS(EI): *m/z* calcd for $C_{13}H_{13}BrN_2O_4$ [M^+]: 340.0059; found, 340.0055. *Ethyl 3-hydroxy-2-((2-methyl-1H-indol-3-yl)methyl)-2-nitropropanoate* (**9d**): yellow oil, FTIR(neat): 3539, 3406, 2984, 1743, 1554, 1462, 1436, 1346, 1218, 1045, 1013, 746 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.95$ (br s, 1H), 7.49 (d, $J = 7.1$ Hz, 1H), 7.23 (d, $J = 7.8$ Hz, 1H), 7.14–7.04 (m, 2H), 4.25 (m, 2H), 4.21 (dd, $J = 6.0$, 7.1 Hz, 1H), 4.13 (dd, $J = 6.0$, 12.2 Hz, 1H), 3.86 and 3.74 (ABq, $J = 15.1$ Hz, 2H), 2.33 (s, 3H), 2.31 (br s, 1H), 1.24 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 166.1$, 135.2, 134.4, 128.9, 121.6, 119.9, 117.9, 110.4, 102.8, 96.6, 63.7, 63.1, 27.9, 13.7, 11.8; HRMS(EI) calcd for $C_{15}H_{18}N_2O_5$ [M^+]: 306.1216; found, 306.1214.