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A General Preparation of β-Substituted Tryptophan Esters

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Abstract : The title compounds **6** have been synthesized in 4 steps from indoles, aldehydes and Meldrum's acid.

With the growing development of combinatorial chemical libraries, more and more attention is paid to the preparation of unnatural α-aminoacids which are one of the useful tools in medicinal chemistry: they can be incorporated in active peptides or peptidomimetics in order to find active conformations[1], especially in the case of tryptophan.[2] β-Substituted tryptophan units can also be found in a few marine natural products.[3]

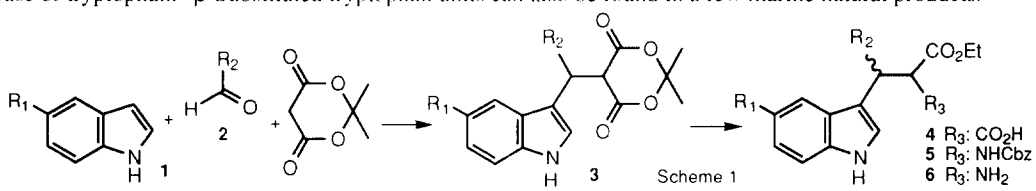


Table 1.

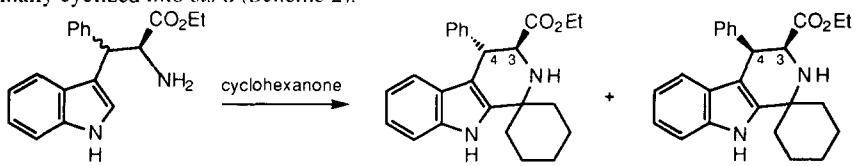
Entry	Indole 1 R_1	Aldehyde 2 R_2	Products (yield, %)[10] 3	4	5	6
a	H	Ph	90	71	76	96
b	H	Bn	80	76	40	71
c	H	(2-ethylprop)-1-yl	75	67	70	67
d	H	cyclohexyl	75	60	82	
e	Br	Bn	83	87	81	70+
f	CN	Ph	38			
g	H	CH_2O-Cbz	90	87	28*	
h	Br	Me	75	70		
j	H	2-furyl	15			
k	H	(2-methylprop-1-en)-1-yl	0			
l	Br	Ph	77	68	45§	98
m	H	(2,6 di-OMe)Ph	82	72	47	69
n	H	piperidino-acetamidyl	39*	63*	26*	78*

* non optimized; § Boc-urethane instead of Cbz-urethane;
+ compound **6b** was isolated:

In continuation of our earlier work on non-sedative analgesics derivating from tryptophan[4], we needed several different β-substituted tryptophan esters in large quantities. All the existing methods suffered from some limitations in yields or technical constraints.[5] Recently, Crich published an elegant approach with a complete control of both stereogenic centers,[6] resulting from a stereocontrolled Michael addition of nucleophiles to a cyclic dehydro-tryptophan tautomer.[5] However, the last steps, *ie.* N-deprotection and C ring cleavage, proved to be troublesome and tedious. Here we suggest a more conventional, but shorter and more economical approach based on indole chemistry. Condensation between indoles **1** aldehydes **2** and Meldrum's acid gave derivatives **3**.[7] Careful cleavage (EtOH, pyridine, 80°C) led to half-esters[8] **4** which underwent Curtius rearrangement after treatment with DPPA[9] in the presence of triethylamine (Scheme 1).

Intermediate isocyanates (not isolated) were then converted into benzyl carbamates **5**, whose hydrogenolysis (H_2, Pd, rt, 1 atm) gave the target compounds **6**, sometimes polluted with urea. Initial condensation was successful with many different aldehydes, except for senecialdehyde (0%), furfural (15%), and slowed down with the deactivated 5-cyanoindole. In the case of 5-bromoderivatives, the last reductive step was accompanied by debromination, which was avoided by using *t*-BuOH instead of benzyl alcohol in the course of the solvolysis of the isocyanate: the resulting Boc-urethane can be converted into amine **6l** by TFA (3h, rt). Finally, a 1:1 mixture of isomers (*erythro* and *threo*) was obtained, which is not a real drawback for our purpose, insofar as we need both diastereoisomers for SAR studies.

Assignment of the relative stereochemistry was conveniently performed in the case of the **6a** mixture, but we guess it can be general. In Pictet-Spengler conditions (cyclohexanone, AcOH, 80°C), one of the diastereoisomers **6a** reacted more quickly to give spiro-β-carboline **7**, whose *trans* stereochemistry was evidenced by the large (9.5 Hz) H^3-H^4 coupling constant. Under more forced conditions, the other isomer **6a** (*erythro*) finally cyclized into *cis* **8** (Scheme 2).



6a (*erythro +threo*) **7** *trans*: $J_H{}^3{}_{-H}{}^4$= 9.5 Hz **8** *cis*: $J_H{}^3{}_{-H}{}^4$=3.5 Hz

Scheme 2

Work is in progress on broadening the scope of this reaction to less reactive aldehydes.

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References and notes :

1. K.E. Kövér, D. Jiao, S. Fang, V.J. Hruby, *J. Org. Chem.*, **1994**, *59*, 991-998. W.M. Kazmierski, Z. Urbanczyk-Lipkowska, V.J. Hruby, *J. Org. Chem.*, **1994**, *59*, 1789-1795.
2. M. Higginbottom, C. Kneen, G.S. Ratcliffe, *J. Med. Chem.*, **1992**, *35*, 1572-1577.
3. P. Crews, J.J. Farias, R. Emrich, P.A. Keifer, *J. Org. Chem.*, **1994**, *59*, 2932-2934; G. Bifulco, I. Bruno, L. Minale, R. Riccio, A. Calignano, C. Débitus, *J. Nat. Prod.*, **1994**, *57*, 1294-1299.
4. J. Lévy, J.Y. Laronze, M. Devissaguet, *Eur. Pat. Appl.* EP 466 548 (1992). (*Chem. Abst.*, **1992**, *116*, 235610b).
5. H.R. Snyder, D.S. Matteson, *J. Am. Chem. Soc.*, **1957**, *72*, 2217-2221 ; U. Schöllkopf, R. Lonsky, P. Lehr, *Liebigs Ann. Chem.*, **1985**, 413-417; S.P. Hollinshead, M.L. Trudell, P. Skolnick, J.M. Cook, *J. Med. Chem.*, **1990**, *33*, 1062-1069; L.W. Boteju, K. Wegner, V.J. Hruby, *Tetrahedron Lett.*, **1992**, *33*, 7491-7494.
6. M. Bruncko, D. Crich, *J. Org. Chem.*, **1994**, *59*, 4239-4249.
7. Y. Oikawa, H. Hirasawa, O. Yonemitsu, *Tetrahedron Lett.*, **1978**, 1759-1762.
8. For a related transformation of functionalized Meldrum's acid into malonic acid half ester, see: M. Chorev, E. Rubini, C. Gilon, U. Wormser, Z. Selinger, *J. Med. Chem.*, **1983**, *26*, 129-135.
9. N. Ninomiya, T. Shioiri, S. Yamada, *Tetrahedron*, **1974**, *30*, 2151-2157.
10. Compounds **4-6** were isolated as diastereomeric (1:1) racemates. **6a** can be considered as a derivative of phenylalanine as well. All compounds were fully characterized by UV, IR, MS, ^{1}H- and ^{13}C-NMR experiments. Yields are given for isolated products. Generally the reactions are univocal, except for entries **j** and **k** where the bis-adduct of aldehyde with indole was the major or the sole product. Spectral data on **6a**: MS (m/z) 308 ($M^{\cdot+}$); UV (MeOH, nm) 290, 288, 220; IR (KBr, cm^{-1}), 3410, 2990, 1730, 1600, 1460; ^{1}H NMR (300MHz, $CDCl_3$, TMS) (less polar = *erythro* isomer) δ 1.05 (t, 3H, J=7.6 Hz, $OCH_2\underline{CH_3}$), 1.60 (s, 2H, NH_2), 4.03 (q, 2H, J=7.6 Hz, $O\underline{CH_2}CH_3$), 4.22 (d, 1H, J=6.7 Hz, $\underline{CH}CO_2Et$), 4.68 (d, 1H, J=6.7 Hz, $\underline{CH}Ph$), 6.95-7.41(m, 10H, aromatic), 8.37 (s, 1H, NH indole); (more polar = *threo* isomer) δ 0.98 (t, 3H, J=7.6 Hz, $OCH_2\underline{CH_3}$), 1.7 (s, 2H, NH_2), 3.95 (q, 2H, J=7.6 Hz, $O\underline{CH_2}CH_3$), 4.23 (d, 1H, J=8.5 Hz, $\underline{CH}CO_2Et$), 4.65(d, 1H, J=8.5 Hz, $\underline{CH}Ph$), 7.0-7.4 (m, 10H, aromatic), 8.37 (s, 1H, indole NH).

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