AN EFFICIENT SYNTHESIS OF 1,2,3,4-TETRASUBSTITUTED PYRROLES VIA INTRAMOLECULAR AZOMETHINE YLIDE [3+2] DIPOLAR CYCLOADDITION#

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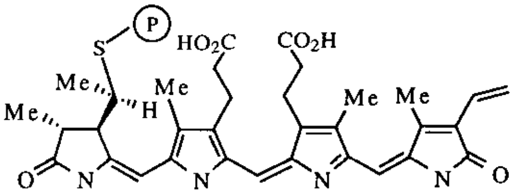
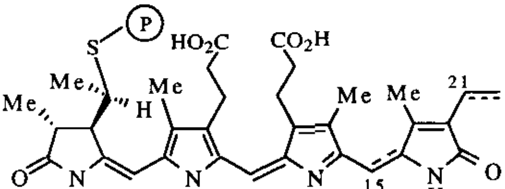
Abstract——A sequence of reactions, involving intramolecular azomethine ylide [3+2] dipolar cycloaddition, was used to efficiently construct 1,2,3,4-tetrasubstituted pyrroles.

Efforts to develop simple and efficient approaches to highly functionalized pyrroles have been stimulated by increasing awareness of the occurrence of these substructures in a wide variety of bioactive natural products, including biliproteins (**1**).[1] Among the strategies developed for synthesis of these rings, those based upon Paal-Knorr cyclization protocol[2] are particularly attractive since it allows simultaneous formation of several bonds in a single operation.



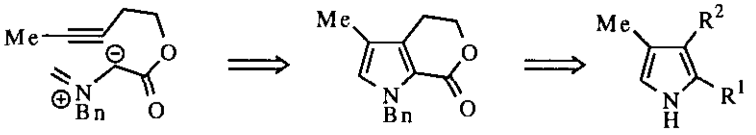
Phytochrome (**1a**)
(P: protein)



Phycocyanin (**1b**) (Δ-15)
Phycoerythrin (**1c**) (Δ-21)

In our first contribution to this area, we describe an approach based upon an intramolecular azomethine ylide [3+2] cycloaddition[3] strategy (**2**→**3**) This approach employs the regiospecific nature of intramolecular [3+2] cycloaddition to establish the desired orientation of substituents destined to occupy the pyrrole nucleus (**4**).

Dedicated to Dr. Arnord Brossi on the occasion of his 70th birthday.

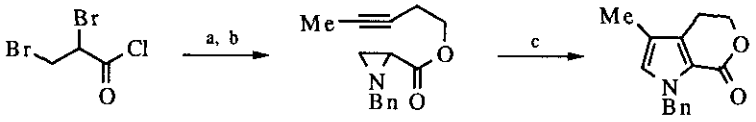


2 3 4

Scheme I

An important advantage of the present strategy is that the required precursors are easily prepared in two steps and in quantitative yield from commercially available starting materials. Esterification of 2,3-dibromopropionyl chloride (**5**) with 3-pentyn-1-ol followed by aziridine formation reaction led quantitatively to **6**.[4]

With **6** in hand, the crucial intramolecular azomethine ylide [3+2] dipolar cycloaddition reaction was attempted. Some of conditions and yields examined for cycloaddition of **6** are listed in **Table I**. In order to determine the influence of temperature on product yield, the cycloaddition was first investigated over the temperature range from 180 °C to 330 °C. As a result of testing, the thermal reaction in *o*-dichlorobenzene at 310 °C for 10 min proceeded quite nicely to provide **3**[4] in 43% yield.[5] The thermolysis of **6** in the presence of radical scavenger was next attempted under various conditions, giving the unsatisfactory result.



5 6 3

Reagents and Conditions: a, MeC≡CCH$_2$CH$_2$OH, K$_2$CO$_3$, THF, room temperature, b, BnNH$_2$, Et$_3$N, toluene, 60 °C (2 steps: 99%), c, see **Table**.

Scheme II

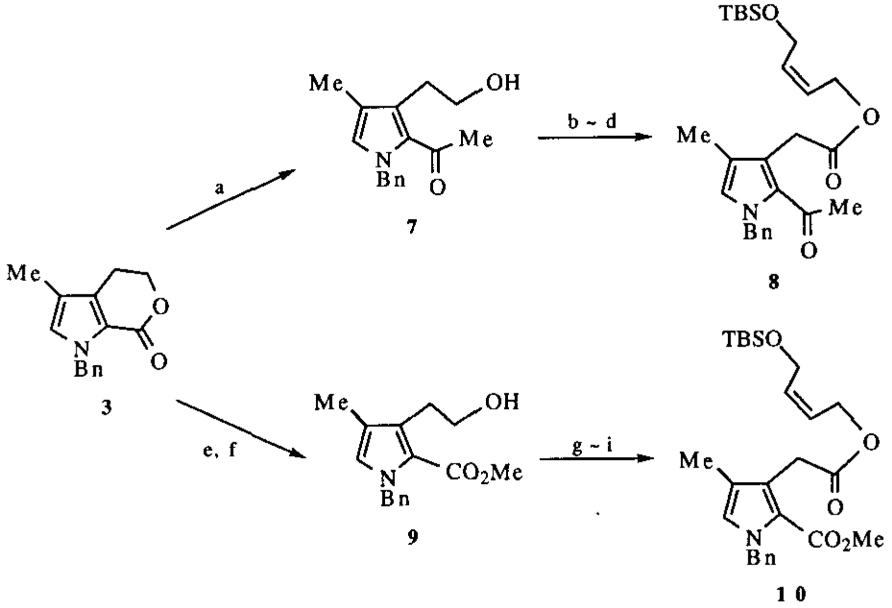
Table I

Conditions and Yields of Intramolecular Azomethine Ylide [3+2] Dipolar Cycloaddition Reaction of **6**

run	additive	temp (°C)	time (min)	yield [a] (%)
1	none	180	60	0
2	none	280	30	33
3	none	310	10	43
4	none	330	10	30
5	MB [b]	310	10	7
6	BMPS [c]	310	10	11

a) The yields of the adduct (**3**) were determined by isolation.
b) Methylene blue
c) 3-*tert*-Butyl-4-hydroxy-5-methylphenyl sulfide

The cycloadduct (**3**) is a or the versatile precursor of highly functionalized pyrroles as illustrated in **Scheme III**. For instance, the transformation of **3** into the keto ester (**8**)[4] was completed by successive methylation (92%), oxidation with PDC, esterification (2 steps: 20%) and silylation (67%), while hydrolysis of **3** followed by consecutive esterification, Jones oxidation, esterification and silylation (5 steps: 20%) afforded the diester (**10**).[4]



Reagents and Conditions: a, MeLi, *THF, -78 °C → -30 °C (92%), b, PDC, DMF, f* c, $HOCH_2CH{=}CHCH_2OH$, DCC, DMAP, CH_2Cl_2 (2 steps: 20%), d, TBSCl, imidazole, DMF (67%), e, LiOH, THF, H_2O, reflux, f, CH_2N_2, Et_2O, 0 °C, g, Jones reagent, Me_2CO, 0 °C, h, $HOCH_2CH{=}CHCH_2OH$, DCC, DMAP, CH_2Cl_2, i, TBSCl, imidazole, DMF (5 steps: 20%).

Scheme III

In conclusion, the feasibility of the intramolecular azomethine ylide [3+2] dipolar cycloaddition approach to the formation of 1,2,3,4-tetrasubstituted pyrroles has been demonstrated. Based upon this strategy, advanced intermediates for the synthesis of biliproteins (**1**) have been readily assembled.

ACKNOWLEDGMENT

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REFERENCES AND NOTES

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4. All new compounds were fully characterized by spectroscopic techniques (^{1}H nmr, ir, ms). ^{1}H Nmr (500 MHz) and ir data for representative compounds are as follows: **Compound (6)**: Ir ($CHCl_3$): 1750 cm^{-1}. ^{1}H Nmr: δ 1.75-1.78 (4H, m), 2.22 (1H, dd, *J*=6.5 and 3.0 Hz), 2.28 (1H, dd, *J*=3.0 and 1.0 Hz), 2.45-2.50 (2H, m), 3.56 (2H, dd, *J*=18.0 and 14.0 Hz), 4.13-4.25 (2H, m), 7.25-7.36 (5H, m). **Compound (3)**: Ir ($CHCl_3$) 1705 cm^{-1}. ^{1}H Nmr: 1.99 (3H, br s), 2.78 (2H, br t, *J*=5.5 Hz), 4.48 (2H, br t, *J*=5.5 Hz), 5.45 (2H, s), 6.66 (1H, s), 7.20-7.32 (5H, m). **Compound (7)**: Ir ($CHCl_3$): 3400 and 1640 cm^{-1}. ^{1}H Nmr: δ 2.04 (3H, s), 2.45 (3H, s), 3.02 (2H, t, *J*=6.5 Hz), 3.78 (2H, br t, *J*=6.5 Hz), 5.43 (2H, s), 6.68 (1H, s), 7.02-7.07 (2H, m), 7.20-7.32 (3H, m). **Compound (8)**: ^{1}H Nmr: δ 0.02 (6H, s), 0.84 (9H, s), 1.97 (3H, s), 2.36 (3H, s), 3.72 (2H, s), 4.20 (2H, dd, *J*=6.5 and 1.5 Hz), 4.63 (2H, br d, *J*=6.5 Hz), 5.39 (2H, s), 5.45-5.51 (1H, m), 5.64-5.70 (1H, m), 6.61 (1H, s), 6.98-7.01 (2H, m), 7.14-7.25 (3H, m). **Compound (9)**: ^{1}H Nmr: δ 2.03 (3H, s), 3.01 (2H, t, *J*=5.5 Hz), 3.75 (3H, s), 3.77 (2H, br t, *J*=5.5 Hz), 5.41 (2H, s), 6.65 (1H, s), 7.04-7.08 (2H, m), 7.21-7.32 (3H, m): **Compound (10)**: ^{1}H Nmr: δ 0.08 (6H, s), 0.90 (9H, s), 2.00 (3H, s), 3.72 (3H, s), 3.77 (2H, s), 4.27 (2H, d, *J*=6.0 Hz), 4.67 (2H, d, *J*=6.5 Hz), 5.47 (2H, s), 5.52-5.59 (1H, m), 5.69-5.75 (1H, m), 6.65 (1H, s), 7.06-7.10 (2H, m), 7.21-7.32 (3H, m).
5. Although this yield is not impressive, it should be noted that triple bond is notoriously unreactive in contrast with double bond.

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