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Unexpected Alkylation Reaction of Amines, Acids and Phenols by Alkyl (triphenylphosphoranylidene)acetates

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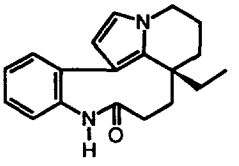
Abstract: *Reaction of methyl (triphenylphosphoranylidene)acetate in methanol with primary and secondary amines led to N-methylated derivatives. Similarly this mixture reacted with acids, phenol and phthalimide to afford methyl esters, anisole and N-methylphthalimide respectively. Treatment of ketolactam 2 by this mixture under high pressure activation gave the rearranged quinolinone 5.*

In the course of an ongoing project directed to the enantioselective synthesis of the cytotoxic agent (+)-rhazinilam **1**,[1] we were facing the problem of annulating the pyrrole ring from the ketolactam **2**.[2] This compound was readily available by ozonolysis of the trifluoroacetic acid salt of pyrido-carbazole **3**, which has been previously prepared as a key intermediate in our total synthesis of (+)-aspidospermidine.[3]



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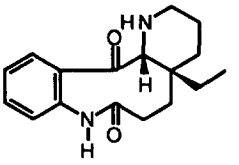

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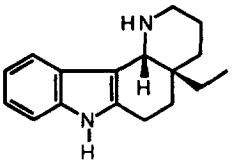

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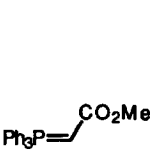
It was our original hope that vinyl Grignard reagent might add to the ketonic group of compound **2**. Unfortunately all attempts at performing this reaction with vinylmagnesium bromide or various other organometallic reagents turned out to be fruitless. In view of the above results, we decided to explore the reaction of a stabilized Wittig reagent under high pressure activation. In the event, treatment of a 4:1, THF/MeOH solution of ketolactam **2** with methyl (triphenylphosphoranylidene)acetate **4** (3 eq, 14 kbar, 50 °C, 48 h) gave a unique less polar compound with a 70 % yield. This product was identified by NMR and MS as being the tetracyclic aminolactame **5**.[4] To our surprise, the gross structure of this compound was no longer the pyrido-benzazonine nucleus of **2**, but instead a rearranged quinolinone. Even more amazingly, *both nitrogen atoms of this product now bore a methyl group.*



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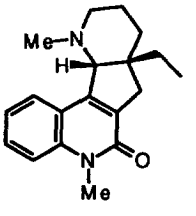

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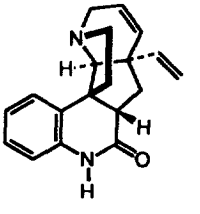
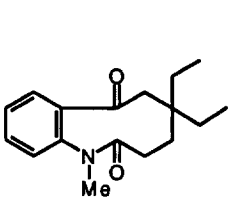


6

The conversion [**2**→ **5**], presumably arose by transannular aldol reaction of the nine-membered ketolactam (Camps reaction).[5] It should be noted that, during a preliminary work, similar transformation was observed. Thus, attempts to prepare the silyl-enol ether of the simplified model ketolactam **7** (2 eq. TMSOTf, 4 eq. Et_3N, CH_2Cl_2, 20 °C) led to a mixture of cyclopenta[c]quinolinone **8**[6] and silyl ether **9** with a 85 % combined yield. The latter was easily converted to **8** by treatment with *p*-TsOH in refluxing toluene.

Since compound **5** exhibits the backbone of the [ABCD] ring system of *Melodinus* alkaloids exemplified by meloscine **6**, the two-step transformation of pyrido-carbazole **3** into quinolinone **5** might offer a new, efficient access to the *Melodinus* carbon core.[7]



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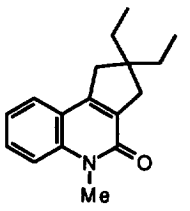

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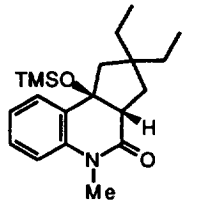

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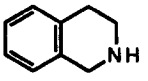
The presence of the two *N*-methyl groups in **5**, attested by two singlets at 2.41 and 3.74 ppm in the ^1H NMR spectrum and two CH_3 signals at 29.4 and 45.3 ppm in the DEPT ^{13}C NMR spectrum, is more puzzling. To gain insight into the origin of this phenomenon we decided to carry out this reaction on a simple secondary amine, namely tetrahydroisoquinoline **10**. When a 4:1, CH_2Cl_2/MeOH solution of amine **10** was left at room temperature for 5 days with 5 eq of methyl (triphenylphosphoranylidene)acetate **4**, *N*-methyl-tetrahydroisoquinoleine **11** was obtained in 60 % yield along with 20 % of amide **12**. The other product of the reaction was triphenylphosphine oxide. When the reaction was run at 0 °C the amount of **12** decreased to 10 %. No reaction occurred without methanol. Conducting the reaction at 50 °C did not increase the rate of conversion of **10** to **11** but instead afforded a larger amount of **12** as well did the use of methanol only. Interestingly enough, adding catalytic amount of *p*-TsOH had no effect on the reaction course whereas the use of a polar solvent such as DMF or CH_3CN slowed down the rate of conversion.



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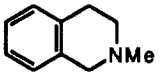

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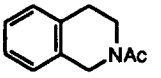


12

The reaction is not limited to cyclic secondary amines, for example *N*-methylbenzylamine **13** afforded dimethylbenzylamine **14** in 70 % yield, along with amide **15** (10 %) and some starting material (20 %). Similarly, benzylamine gave mainly **13** and *N*-benzylacetamide **17**, along with small amounts of **14** and **15**.

13

14

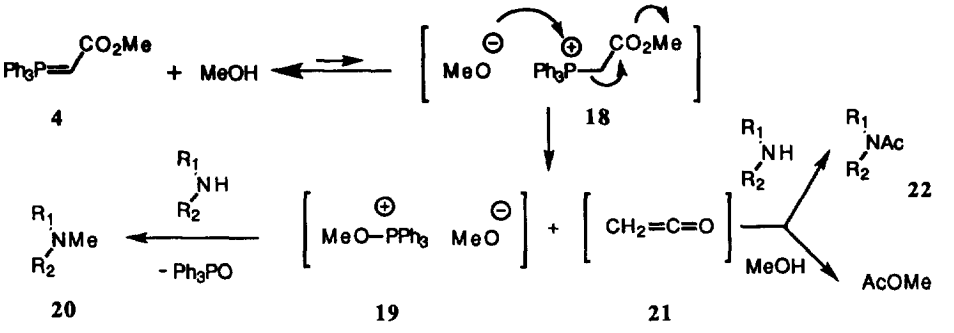
15

16

17

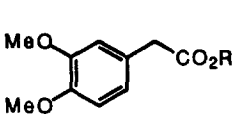
A plausible mechanism that might explain these results is depicted in **scheme 1**. Protonation of the ylide **4** by methanol might lead to the phosphonium salt **18** that could dissociate into ketene and methoxy-triphenyl

phosphonium salt **19**. Ketene would rapidly react with methanol to give methylacetate and with the amine to produce the corresponding acetamide **22**.[8] On an other hand the reaction of the amine with **19** should lead to the *N*-methylated amines **20**. Indeed, it is well known that alkoxytriphenylphosphonium salts of type **19** are the active species in the Mitsunobu reaction[9] and so, react with acids, imides and other acidic compounds. The fact that the Mitsunobu reaction with amines has been previously reported further probes our hypothesis.[10]

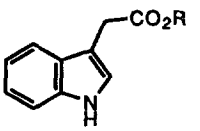


scheme 1

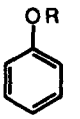
The possible implication of the salt **19** in the methylation of amines suggests that ylide **4** in MeOH might alkylate other nucleophiles. To test this hypothesis, carboxylic acids **23a** and **24a** were treated with 3 eq of ylide **4** in methanol. To our delight, the corresponding methyl esters **23b** and **24b** were obtained in 80-85 % yields by standing one day at 20 °C. Similarly, phenol and phthalimide underwent methylation to give anisole **25b** and *N*-methylphthalimide **26b**, respectively.



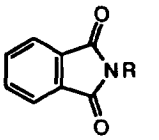
23a : R = H
23b : R = Me
23c : R = Et



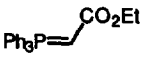
24a : R = H
24b : R = Me



25a : R = H
25b : R = Me



26a : R = H
26b : R = Me



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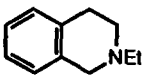

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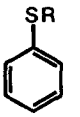

29a : R = H
29b : R = Me

30

We briefly also examined the reactions of ethyl (triphenylphosphoranylidene)acetate **27** with previous nucleophiles. Acid **23a**, on treatment with ylide **27** in CH_2Cl_2/EtOH, produced ethyl ester **23c**, although the reaction was slower than with the corresponding methyl ylide **4** (50 °C, 2 days). Such a decrease in the rate of the esterification might reflect that the dissociation [**18** → **19**] is the rate limiting step of this reaction. When amine **10** was treated by ylide **27** (4:1, CH_2Cl_2/EtOH, 20 °C, one week), *N*-ethyl-tetrahydoisoquinoline **28**

was obtained in 60 % yield along with starting material and a minor amount of amide **12**. The presence of the latter product in the reaction mixture supports the transient formation of ketene, as proposed in **scheme 1**.

Finally, thiophenol reacted with **4** in 4:1, CH_2Cl_2/MeOH to give only trace amount of the expected thioanisole **29b**, the main compounds being thioketal **30** [11] (80 % yield) and triphenylphosphine oxide. Interestingly the same products were obtained when ylide **27** was employed in ethanol, showing that the carbon atoms of the alcohol were not incorporated into thioketal **30**. So far the origin of this compound remains unclear.

Acknowledgments: I thank Professor J. d'Angelo, Drs. F. Dumas and C. Cavé for enlightening suggestions, and Dr J. Mahuteau for her help in elucidating the structure of compound **5**.

Notes and References

1. Abraham, D. J.; Rosenstein, R. D. *Tetrahedron Lett.*, **1972**, *10*, 909-912; Thoison, O.; Guénard, D.; Sévenet, T.; Kan-Fan, C.; Quirion, J.-C.; Husson, H.-P.; Deverrre, J.-R.; Chan, K.-C.; Potier, P. *C. R. Acad. Sc. Paris*, **1987**, *304*, Sér. II, 157-160.
2. **2**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.50 (broad s, 1H), 7.65 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.52 (td, *J* = 7.6, 1.8 Hz, 1H), 7.42 (td, *J* = 7.5, 1.1 Hz, 1H), 7.25 (dd, *J* = 7.5, 1.1 Hz, 1H), 4.69 (s, 1H), 3.1 (d, 12.9 Hz, 1H), 2.5 (m, 2H), 1.90-1.65 (m, 2H), 1.6-0.9 (m, 7H), 0.7 (m, 1H), 0.55 (t, *J* = 6.9 Hz, 3H); IR (neat, cm^{-1}) ν: 3335, 3071, 1666, 1596.
3. Desmaële, D.; d'Angelo, J. *J. Org. Chem.*, **1994**, *59*, 2292-2303.
4. **5**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (dd, *J* = 7.9, 0.9 Hz, 1H), 7.51 (m, 1H), 7.37 (d, *J* = 8.5 Hz, 1H), 7.22 (dd, *J* = 7.9, 7.1 Hz, 1H), 3.74 (s, 3H), 3.53 (s, 1H), 2.97 (d, *J* = 16.5 Hz, 1H), 2.75 (m, 1H), 2.59 (d, *J* = 16.5 Hz, 1H), 2.41 (s, 3H), 2.29 (ddd, *J* = 11.2, 9.4, 2.2 Hz, 1H), 1.9-1.6 (m, 3H), 1.5 (m, 3H), 0.83 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$), δ 161.6(C), 150.8(C), 139.8(C), 133.9(C), 129.2(CH), 125.7(CH), 121.5(CH), 120.9(C), 114.4(CH), 73.9(CH), 53.2(CH_2), 46.0(C), 45.3(CH_3), 37.2(CH_2), 32.2(CH_2), 30.0(CH_2), 29.4(CH_3), 20.3(CH_2), 8.8(CH_3); IR (neat, cm^{-1}) ν: 3060, 2937, 1651, 1595, 1564, 1455; MS (70 eV) m/z: 296($M^{+\cdot}$,71), 281(80), 267(44), 253(100), 226(29), 210(20), 198(18), 124(34).
5. Gale, D. J.; Wilshire, J. F. K. *Aust. J. Chem.*, **1974**, *27*, 1295-1308. For a related example see: Winterfeldt, E.; Korth, T.; Pike, D.; Boch, M. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 289-290.
6. **8**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.60-7.20 (m, 4H), 3.64 (s, 3H), 2.81 (s, 2H), 2.67 (s, 2H), 1.43 (q, *J* = 7.3 Hz, 2H), 0.77 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$), δ 161.6(C), 148.8(C), 139.9(C), 131.9(C), 129.3(CH), 125.1(CH), 121.7(CH), 119.6(C), 114.4(CH), 44.9(C), 42.7(CH_2), 41.8(CH_2), 31.7(2CH_2), 29.2(CH_3), 8.8(2CH_3); IR (neat, cm^{-1}) ν: 2969, 1645, 1598, 1460.
7. Palmisano, G.; Danieli, B.; Lesma, G.; Riva, R.; Riva, S. *J. Org. Chem.*, **1984**, *49*, 4138-4143.
8. The formation of amide **12** by reaction of amine **10** with methylacetate must be rejected because the latter compound failed to react with a large excess of methylacetate for one week in methanol at room temperature.
9. Mitsunobu, O. *Synthesis* **1981**, 1-28; Camp, D.; Jenkins, I. *J. Org. Chem.*, **1989**, *54*, 3045-3049.
10. Sammes, P., G.; Smith, S. *J. Chem. Soc., Perkin Trans. I* **1984**, 2415-2419. Treatment of a mixture of tetrahydroisoquinoline **10** and triphenyphosphine in CH_2Cl_2/methanol with diethylazodicarboxylate gave *N*-methylated amine **11** in 35 % yield.
11. Thioketal **29** was identified by comparison with an authentic sample, made by treatment of paraformaldehyde with thiophenol (BF_3-OEt_2 cat., CH_2Cl_2, 20 °C, 3 h).

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