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Reaction of Cyclohexanones Imines with Substituted Nitroolefins. New Synthesis of Tetrahydroindole Derivatives

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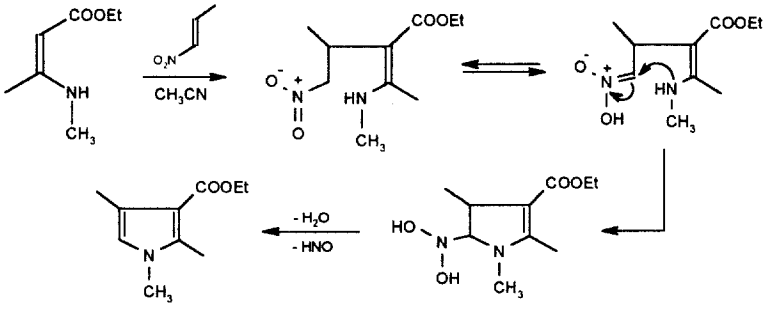
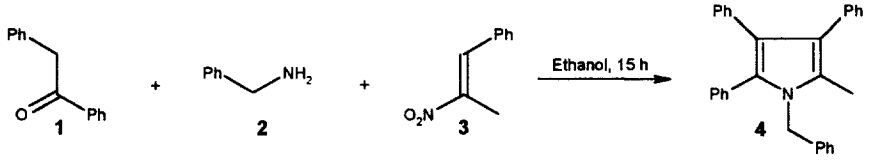
ABSTRACT: The Michael-type addition of cyclohexanones imines, reacting as their secondary enamine tautomers, to β-substituted nitroolefins is followed by a cyclization reaction with elimination of the nitro group to afford substituted tetrahydroindoles. When a 2-methylcyclohexanone imine is reacted, an unexpected inversion of the regioselectivity is observed when compared with β-substituted ethylenic esters, thus allowing to obtain also substituted tetrahydroindoles.

Keywords: Imines ; Michael reactions ; Regioselection ; Indoles.

A reaction involving the addition of secondary enaminoesters to 1-nitropropene followed by an intramolecular displacement of the nitro group by the amino group to yield pyrroles was disclosed in the 50's[1,2] (Example given in the following Scheme). This interesting reaction was scarcely studied afterwards.[3,4]



As imines are known to react through their secondary enamine form (present in undetectable concentration at equilibrium) in Michael-type reactions[5], we thought that Grob's reaction could possibly be extended to simple imines. In fact, a later example by Meyer[4] involved the reaction of a mixture of deoxybenzoin **1**, benzylamine **2**, and nitroolefin **3** to give the pyrrole **4** in low yield but the intermediacy of an imine or a secondary enamine was not suggested.



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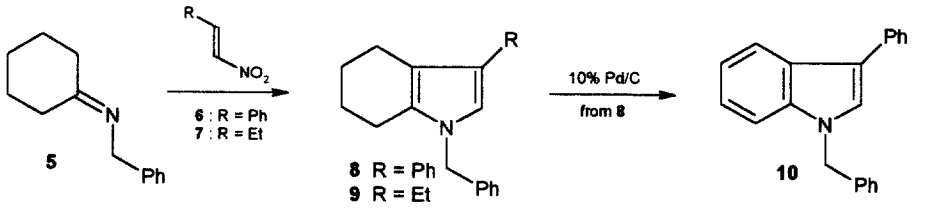
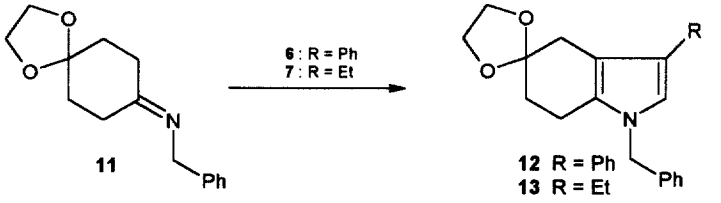
Indeed, one can anticipate in this case that the low yield observed is due to the fact that nucleophilic addition of benzylamine **2** to nitroolefin **3** could compete with imine formation. In order to show that this reaction must proceed through Michael reaction of the secondary enamine tautomer of the imine we decided to try the reaction with cyclohexanones imines (for synthetic purpose) in order to obtain cyclized compounds of the tetrahydroindole type.

Thus, when imine **5**[8] was reacted with one equivalent of trans-β-nitrostyrene **6** (0.5 M in toluene, 0 °C then rt 1h) we obtained after chromatography (SiO_2, EtOAc/hexane 2:98) the tetrahydroindole **8**[9] in 70% yield. Its structure was confirmed by the dehydrogenation reaction[10] of **8** (0.4 M in xylene, 10% of 10% Pd/C, 140 °C, 2d) yielding the known[11] 1-benzyl-3-phenyl-1*H*-indole (**10**) in 76% yield.



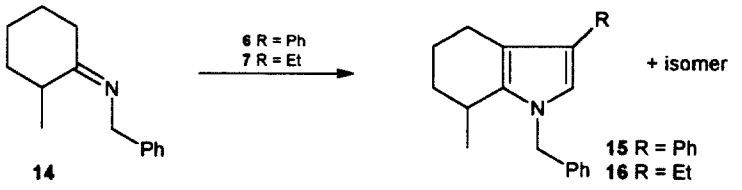
The analogous tetrahydroindole **9**, substituted by an ethyl group, was obtained in the same conditions from imine **5** and 1-nitrobutene (**7**).[12] A GC-MS analysis of the reaction medium showed the presence in appreciable quantity of by-products generated by the addition of the nitroolefin to the benzylamine issued from the hydrolysis of the starting imine by the water generated in the cyclization step. The use of powdered 4 Å molecular sieves (2:1 w/w) in the reaction medium allowed to suppress this undesirable reaction. In these conditions, the tetrahydroindole **9**[9] was obtained in 47% yield[13] after purification through chromatography (SiO_2, EtOAc/hexane 2:98).

We have then tested this reaction with the functionalized imine **11**[8] in order to obtain the corresponding tetrahydroindoles bearing a masked carbonyl function on the 5 position. Thus, imine **11** was reacted with 1.1 equivalent of trans-β-nitrostyrene (**6**) (0.5 M in toluene, 2:1 w/w 4 Å molecular sieves[14], rt 24 h) to give the expected tetrahydroindole **12**[9] as a solid in 90% yield. In analogous manner, with one equivalent of 1-nitrobutene **7** (0.5 M in toluene, 2:1 w/w 4 Å molecular sieves[14], 0 °C then rt 5h), imine **11** yielded the tetrahydroindole **13**[9] in 63% yield.



We have also studied the case of 2-methyl(benzylimino)cyclohexane (**14**)[8] with the interesting problem of the regioselectivity of the reaction. Indeed, the Michael addition could occur either at the substituted α-carbon atom of the imine or at the unsubstituted one. Since the double bound of the nitroolefins **6** and **7** is substituted[15], one could anticipate that the reaction would mainly proceed towards the substituted carbon atom but that a regioisomer would be also formed.

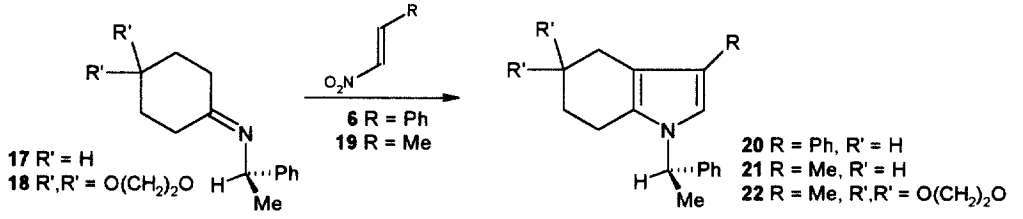
These reactions were performed in one hand with one equivalent of trans-β-nitrostyrene and on the other hand with one equivalent of 1-nitropropene (5 M and 0.5 M respectively in toluene, rt 16h). In both cases, a GC-MS analysis of the reaction mediums showed the presence of two isomeric compounds in the same ratio of *ca.* 75:25. Both major products were isolated through chromatography (SiO_2, EtOAc/hexane 10:90) in respectively 51% and 28%[13] yield and identified as tetrahydroindoles **15** and **16**.[9,16]



Therefore the addition of olefins **6** and **7** occurred mainly on the unsubstituted position of imine **14** with *unexpected inversion* of the regioselectivity observed in the case of methyl crotonate.[6c]

Finally, using chiral imines **17** and **18**, we have tested the possibility of obtaining tetrahydroindoles bearing a chiral moiety on the nitrogen atom which could be models for precursors of useful building blocks.

Thus, imine **17**[8] was first reacted with one equivalent of trans-β-nitrostyrene **6** (1 M in toluene, rt 1h) to give the tetrahydroindole **20**[9] isolated after chromatography (SiO_2, EtOAc/hexane 1:8) in 70% yield. In the presence of one equivalent of 1-nitropropene **19**[12] (1.6 M in toluene, 0 °C then rt 1h) the same imine **17** yielded the corresponding tetrahydroindole **21**[9] in 35% yield.[13] Starting from the functionalized imine **18**[8] the same nitroolefine **19** (1 equivalent, 1.6 M in toluene, 0 °C then rt 1h) gave the corresponding functionalized chiral tetrahydroindole **22**[9] in 60% yield after chromatography (SiO_2, EtOAc/hexane 1:4).



In conclusion, we have reported that imines, *via* their enamine tautomers, have similar behaviours as β-enaminoesters, *i.e.* Michael additions to nitroolefins followed by cyclization with elimination of water and hyponitrous acid to generate tetrahydroindoles.

REFERENCES AND NOTES

1 Grob C.A., Camenisch K. *Helvetica Chimica Acta.* **1953**, *36*, 49-58.

2 Grob C.A., Schad H.P. *Helvetica Chimica Acta.* **1955**, *38*, 1121-1127.

3 Gomez-Sanchez A., Mancera M., Rosado F., Bellanato J. *J. Chem. Soc. Perkin I* **1980**, 1199-1205.

4 Meyer H. *Liebigs Ann. Chem.* **1981**, 1534-1544.

5 These Michael reactions were performed with linear or cyclic imines[6] and later extended to chiral imines.[7]

6 (a) Pfau M., Ribière C. *J. Chem. Soc., Chem. Commun.* **1970**, 66-67. (b) Pfau M., Ughetto-Monfrin J. *Tetrahedron* **1979**; *35*, 1899-1904 and references therein. (c) Pfau, M.; Tomas, A.; Lim, S.; Revial, G. *J. Org. Chem.* **1995**, *60*, 1143-1147.

7 Pfau, M.; Revial, G.; Guingant, A.; d'Angelo, J. *J. Am. Chem. Soc.* **1985**, *107*, 273-274. Jabin, I.; Revial, G.; Melloul, K.; and Pfau, M. *Tetrahedron: Asymm.* **1997**, *8*, 1101-1109 and reference 1 included.

8 Cyclohexanones imines were obtained from the corresponding cyclohexanones and primary amines in toluene solution at reflux in a Dean Stark water separator for 24 h.

9 **8**: oil, $Eb_{0.02}$ 140-150 °C (bath temperature). EIMS *m/z* (rel int) 287 (M^+, base), 286 (27), 259 (37), 258 (51), 196 (14), 141 (12), 91 (69). IR (neat) 1600, 1550, 1530 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.6 to 1.8 (m, 4H), 2.36 (dd, $J_1 \approx J_2 \approx 6$ Hz, 2H), 2.63 (dd, $J_1 \approx J_2 \approx 6$ Hz, 2H), 4.85 (s, 2H), 6.68 (s, 1H), 6.95 to 7.4 (m, 10H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.96, 22.93, 23.53, 23.71, 49.98, 115.9, 117.3, 122.3, 124.9, 126.6 (2C), 126.7 (2C), 127.3, 128.3 (2C), 128.7 (2C), 129.1, 136.5, 138.1.

9: oil, EIMS *m/z* (rel int) 239 (M^+, 81), 238 (17), 224 (58), 211 (36), 210 (43), 196 (12), 91 (base), 77 (15), 65 (27). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10 (t, J = 7.0 Hz, 3H), 1.35 to 1.85 (m, 4H), 2.30 to 2.46 (m, 6H), 4.81 (s, 2H), 6.27 (s, 1H), 6.94 to 7.30 (m, 5H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.51, 18.41, 21.52, 21.72, 23.17, 23.34, 49.63, 115.8, 116.4, 123.1, 126.6 (2C), 126.9, 127.3, 128.5 (2C), 136.6.

12: solid, mp 122 °C, EIMS *m/z* (rel int) 345 (M^+, 52), 300 (2), 284 (2), 272 (2), 260 (22), 259 (base), 258 (40), 91 (48). IR (nujol) 1595, 1530 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.90 (dd, $J_1 \approx J_2 \approx 6.5$ Hz, 2H), 2.60 (dd, $J_1 \approx J_2 \approx 6.5$ Hz, 2H), 2.90 (s, 2H), 3.90 to 3.95 (m, 4H), 4.90 (s, 2H), 6.70 (s, 1H), 7.00 to 7.35 (m, 10H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.11, 31.30, 34.04, 50.32, 64.50 (2C), 109.1, 113.5, 118.5, 122.3, 124.9, 126.6 (2C), 126.7 (2C), 127.2, 127.4, 128.2 (2C), 128.6 (2C), 136.1, 137.7. Anal. Calcd for $C_{23}H_{23}NO_2$: C, 79.97; H, 6.71; N, 4.06. Found: C, 79.99; H, 6.76; N, 4.10.

13: oil, $Eb_{0.02}$ 160 °C (bath temperature), EIMS *m/z* (rel int) 297 (M^+, 39), 212 (17), 211 (base), 210 (30), 196 (18), 182 (10), 91 (72). IR (neat) 1600, 1550, 1530 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10 (t, J = 7.5 Hz, 3H), 1.87 (dd, $J_1 \approx J_2 \approx 6$ Hz, 2H), 2.35 (q, J = 7.5 Hz, 2H), 2.55 (dd, $J_1 \approx J_2 \approx 6$ Hz, 2H), 2.65 (s, 2H), 3.85 to 4.0 (m, 4H), 4.85 (s, 2H), 6.30 (s, 1H), 6.95 to 7.0 (m, 2H), 7.15 to 7.30 (m, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.42, 18.42, 20.03, 31.58, 32.47, 50.02, 64.45 (2C), 109.3, 114.2, 117.2, 123.0, 125.9, 126.6 (2C), 127.1, 128.5 (2C), 138.6.

15: oil, EIMS *m/z* (rel int) 301 (M^+, 51), 287 (24), 286 (base), 91 (72). IR (neat) 1600 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.07 (dd, J_1 = 7 Hz, J_2 = 1 Hz, 3H), 1.50 to 1.85 (m, 4H), 2.50 to 2.80 (m, 3H), 4.93 (s, 2H), 6.61 (s, 1H), 6.9 to 7.4 (m, 10H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 19.30, 21.10, 23.81, 26.18, 31.16, 49.83, 115.2, 118.1, 122.2, 124.9, 126.6 (2C), 126.7 (2C), 127.3, 128.3 (2C), 128.6 (2C), 133.7, 136.6, 138.4. The mass spectrum of the minor isomer of **15** (**i**): EIMS *m/z* (rel int) 301 (M^+, 28), 287 (23), 286 (base), 91 (96).

16: oil, EIMS *m/z* (rel int) 253 (M^+, 29), 239 (19), 238 (base), 91 (23). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.05 (d, J = 7 Hz, 3H), 1.10 (t, J = 7 Hz, 3H), 1.50 to 1.60 (m, 1H), 1.60 to 1.80 (m, 4H), 2.25 to 2.50 (m, 3H), 2.65 to 2.75 (m, 1H), 4.88 (s, 2H), 6.18 (s, 1H), 6.90 to 7.00 (m, 2H), 7.10 to 7.25 (m, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.18, 18.45, 18.96, 21.01, 21.78, 26.03, 31.44, 49.49, 115.7, 116, 5, 123.0, 126.5 (2C), 127.0, 128.4 (2C), 132.5, 139.0. The mass spectrum of the minor isomer of **16** (**ii**): EIMS *m/z* (rel int) 253 (M^+, 18), 239 (19), 238 (base), 91 (37).

20: oil, EIMS *m/z* (rel int) 301 (M^+, base), 197 (65), 196 (18), 169 (60), 168 (24), 105 (82). IR (neat) 1600, 1525 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.5 to 1.75 (m, 4H), 1.65 (d, J = 7 Hz, 3H), 2.05 to 2.2 (m, 1H), 2.35 to 2.45 (m, 1H), 2.60 (bs, 2H), 5.07 (q, J = 7 Hz, 1H), 6.82 (s, 1H), 6.90 to 7.40 (m, 10H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 22.30, 22.37, 23.11, 23.67, 23.96, 54.77, 113.9, 115.9, 122.1, 125.0, 125.9 (2C), 126.8 (2C), 127.2, 128.4 (2C), 128.7 (2C), 129.4, 136.9, 143.6.

21: oil, EIMS *m/z* (rel int) 239 (M^+, base), 135 (62), 134 (23), 107 (93), 106 (17), 105 (84). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.65 to 1.75 (m, 4H), 1.75 (d, J = 7 Hz, 3H), 2.02 (d, J = 0.7 Hz, 3H), 2.15 to 2.25 (m, 1H), 2.35 to 2.45 (m, 3H), 5.15 (q, J = 7 Hz, 1H), 6.50 (s, 1H), 6.9 à 7.1 (m, 2H), 7.16 to 7.34 (m, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 9.90, 21.36, 21.97, 22.08, 23.19, 23.44, 54.19, 113.3, 115.4, 117.0, 125.7 (2C), 126.8, 127.9, 128.4 (2C), 143.9.

22: oil, EIMS *m/z* (rel int) 297 (M^+, 78), 212 (16), 211 (base), 210 (11), 120 (15), 108 (10), 107 (88), 106 (19), 105 (84). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.75 (d, J = 7 Hz, 3H), 1.82 to 1.90 (m, 2H), 1.99 (s, 3H), 2.35 to 2.45 (m, 1H), 2.55 to 2.70 (m, 1H), 2.68 (s, 2H), 3.85 to 4.05 (m, 4H), 5.12 (q, J = 7 Hz, 1H), 6.50 (s, 1H), 7.0 to 7.05 (m, 2H), 7.15 to 7.40 (m, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 10.01, 20.31, 22.23, 31.73, 32.39, 54.73, 64.51, 64.57, 109.5, 114.77, 114.83, 115.5, 125.8 (2C), 126.0, 127.0, 128.6 (2C), 143.8.

10 Madsen, J.O.; Lawesson, S.-O. *Bull. Soc. Chim. Belg.* **1976**, *85*, 819-828.

11 Zordrager, J.; Broekhof, L.J.M.; Van der Gen, A. *Rec. Trav. Chim. Pays-Bas* **1989**, *108*, 441-444. Supplementary data: EIMS *m/z* (rel int) 283 (M^+, base), 192 (30), 191 (5), 165 (14). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 50.03, 110.0, 117.3, 119.96, 120.03, 122.06, 125.73, 125.82, 126.33, 126.81 (2C), 127.27 (2C), 127.62, 128.66 (2C), 128.72 (2C), 135.43, 137.01, 137.10.

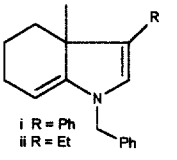
12 Nitroolefins **7** and **19** were prepared according to the method of Mc Murry: Melton, J.; Mc Murry, J.E. *J. Org. Chem.* **1975**, *40*, 2138-2139.

13 This tetrahydroindole derivative is a somewhat unstable oily compound accounting for the observed moderate yield.

14 Molecular sieves were used since by-products were observed in this case.

15 With unsubstituted electrophilic olefins like MVK or acrylate esters, the Michael reaction occurs almost exclusively at the most substituted α-carbon atom of cyclanones imines. However, the same reaction performed with substituted electrophilic olefins (methacrylate and crotonate esters) gives 20-30% of regioisomers arising from reaction at the less substituted α-carbon atome.[6c]

16 In both cases the unstable minor isomers could not be isolated. However, because of the very high similarity of their mass spectrum respectively with those of tetrahydroindoles **15** and **16**, it is highly probable that these compounds are bicyclic adducts **i** and **ii**, arising from "normal" adducts, *i.e.* those which are formed by the attack on the more substituted α-carbon atom of imine **14**.



i R = Ph
ii R = Et