Dakin-West Synthesis of β -Aryl Ketones

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1- General

Reactions were done in 100 mL, 3-necked round-bottom flasks, equipped with a condenser and two valved gas inlet adaptors capped with septa. A hypodermic needle, inserted through one of the septa and reaching below the surface of the solution, was used to bubble N₂ through the reaction mixture during the reaction. NMR spectra were calibrated using TMS and CDCl₃ for both ¹H NMR and ¹³C NMR. NMR spectra are of the product mixtures—the aryl alkyl ketones and their respective enol esters. GC/MS were collected using samples dissolved in methylene chloride. In every case, the GC/MS data were consistent with the presence of the proposed compounds in the product mixture. Phenyl-2-propanone, 1,3-diphenyl-2-propanone, 4-phenyl-2-butanone, 1,5-diphenyl-3-pentanone, 1-(4-methoxyphenyl)-2-propanone, 1,3-bis(4-methoxyphenyl)-2-propanone, 3-phenyl-2-pentanone, 1-(4-nitrophenyl)-2-propanone and 1,3-bis(4-nitrophenyl)-2-propanone have been previously characterized.¹⁻⁵

2- Product characterization

Phenyl-2-propanone and its enol esters: Phenylacetic acid (6.81 g, 0.05 mol) combined with acetic anhydride (25 mL, 0.25 mol) in the presence of 1-methylimidazole (2.0 mL, 0.025 mol) formed phenyl-2-propanone and 1,3-diphenyl-2-propanone (yield: 5.97 g, 93%). Phenyl-2-propanone was the major fraction (94%). Yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 2.15 (s, 3H), δ 3.69 (s, 2H), δ 7.19-7.31 (m, 5H); ¹³C NMR (100 MHz, CDCl₃) δ 29.4, 51.2, 127.2, 128.4, 128.8, 134.4, 206 (Figures 1 and 2); GC/MS *m/z* 134 (M⁺). We found that the enol esters of phenyl-2-propanone formed during the work-up of the reaction. ¹H NMR (400 MHz, CDCl₃) δ 1.86 (s, 3H), δ 2.06 (s, 3H), δ 5.94 (s, 1H), δ 7.19-7.31 (m, 5H). The concentrations of the phenyl-2-propanone enol esters were too low to be detected by ¹³C NMR. GC/MS *m/z* 176 (M⁺).

1,3-diphenyl-2-propanone and its enol esters: Phenylacetic acid (6.81 g, 0.05 mol) combined with acetic anhydride (25 mL, 0.25 mol) in the presence of TEA (7 mL, 0.05 mol) formed 1,3-diphenyl-2-propanone and phenyl-2-propanone (yield: 3.84 g, 73 %).

1,3-diphenyl-2-propanone was 94% of the product mixture. Yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 3.70 (s, 4 H), δ 7.19-7.31 (m, 10H); ^{13}C NMR (100 MHz, CDCl_3) δ 49, 127, 128, 128, 134, 206; GC/MS m/z 210 (M^+). We found that the enol esters of 1,3-diphenyl-2-propanone formed during the work-up of the reaction. ^1H NMR (400 MHz, CDCl_3) δ 2.26 (s, 3H), δ 3.59 (s, 3H), δ 5.93 (s, H), δ 7.21-7.28 (m, 5H). The concentrations of the 1,3-diphenyl-2-propanone enol esters were too low to be detected by ^{13}C NMR. GC/MS m/z 254 (M^+).

4-phenyl-2-butanone and 1,5-diphenyl-3-pentanone: Hydrocinnamic acid (7.90 g, 0.05 mol) was combined with acetic anhydride (25 mL, 0.25 mol) in the presence of 1-methylimidazole (4.0 mL, 0.05 mol) and heated to reflux for 48 hours. The products of this reaction were 4-phenyl-2-butanone (96%) and 1,5-diphenyl-3-pentanone (4%) (yield = 3.64 g, 48 %). Light yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 2.16 (s, 3H), δ 2.77 (t, $J = 7.2$ Hz, 3H), δ 2.89 (t, $J = 7.6$ Hz, 3H), δ 7.17-7.25 (m, 5H). ^{13}C NMR (100 MHz, CDCl_3) δ 30.2, 31.0, 45.3, 126.2, 128.4, 128.6, 141.1, 206.1 (Figures 3 and 4) GC/MS m/z 148 (M^+). The concentration of 1,5-diphenyl-3-pentanone was too low to detect by NMR; GC/MS m/z 238 (M^+). Figure 4 also shows peaks from ethyl acetate used in purification

4-methoxyphenyl-2-propanone and 1,3-bis(4-methoxyphenyl)-2-propanone:

4-methoxyphenylacetic acid (8.32 g, 0.05 mol) combined with acetic anhydride (25 mL, 0.25 mol) in the presence of 1-methylimidazole (2.0 mL, 0.025 mol) formed 4-methoxyphenyl-2-propanone as the major product (95%) and 1,3-bis(4-methoxyphenyl)-2-propanone as the minor product (5%) (yield = 6.74 g, 83%; 100% by ^1H NMR); Yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 2.12 (s, 3H), δ 3.63 (s, 2H), δ 3.76 (s, 3H), δ 6.85 (d, $J = 8.4$ Hz, 2H), δ 6.85 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 29.3, 50.1, 55.3, 114.3, 126.4, 130.5, 158.7, 207.0 (Figures 5 and 6); GC/MS m/z 164 (M^+). The concentration of 1,3-bis(4-methoxyphenyl)-2-propanone was too low to be detected by NMR; GC/MS m/z 270 (M^+).

3-phenyl-2-pentanone: 2-phenylbutanoic acid (8.21 g, 0.05 mol) combined with acetic anhydride (25 mL, 0.25 mol) in the presence of 1-methylimidazole (8.0 mL, 0.1 mol) and heated to reflux formed 3-phenyl-2-pentanone (yield = 0.48 g, 6 %). ^1H NMR (400 MHz, CDCl_3) δ 0.83 (t, J = 7.2 Hz, 3H), δ 1.78 (m, 2H), δ 2.03 (s, 3H), δ 3.51 (t, J = 7.6 Hz, 1H), δ 7.26-7.32 (m, 5H). ^{13}C NMR (100 MHz, CDCl_3) δ 12.2, 25.0, 29.2, 61.6, 127.3, 128.3, 128.9, 138.9, 208.7. (Figures 7 and 8) Figure 8 also shows peaks from acetate contaminant.

4-nitrophenyl-2-propanone and 1,3-bis(4-nitrophenyl)-2-propanone: 4-nitrophenylacetic acid (9.08 g, 0.05 mol) combined with acetic anhydride (25 mL, 0.25 mol) in the presence of 1-methylimidazole (2.0 mL, 0.025 mol) formed 4-nitrophenyl-2-propanone (96%) and 1,3-bis(4-nitrophenyl)-2-propanone (4%) (yield = 100% by ^1H NMR). Figures 9 and 10 are ^1H NMR (400 MHz, CDCl_3) spectra of the reaction mixture at the beginning and end of the reaction. Peaks from 4-nitrophenyl-2-propanone; δ 2.10 (s, 3H), δ 3.87 (s, 2H), δ 7.5 (m, 2H), δ 8.2 (m, 2H); peaks from 1,3-bis(4-nitrophenyl)-2-propanone δ 3.89 (s, 4H), δ 7.5 (m, 2H), δ 8.2 (m, 2H).

^1H NMR and ^{13}C NMR spectra

Figure 1: ^{13}C NMR spectrum of the products of the MIM-catalyzed reaction of phenylacetic acid and acetic anhydride: phenyl-2-propanone, its enol esters and 1,3-diphenyl-2-propanone.

Figure 2: ^1H NMR spectrum of the products of the MIM-catalyzed reaction of phenylacetic acid and acetic anhydride: phenyl-2-propanone, its enol esters and 1,3-phenyl-2-propanone

Figure 3: ^{13}C NMR spectrum of the products of the MIM-catalyzed reaction of hydrocinnamic acid with acetic anhydride: 4-phenyl-2-butanone and 1,5-diphenyl-3-pentanone.

Figure 4: ^1H NMR spectrum of the products of the MIM-catalyzed reaction of hydrocinnamic acid and acetic anhydride: 4-phenyl-2-butanone and 1,5-diphenyl-3-pentanone.

Figure 5. ^1H NMR spectrum of the products of the MIM-catalyzed reaction of 4-methoxyphenylacetic acid with acetic anhydride: 4-methoxyphenyl-2-propanone and 1,3-bis(4-methoxyphenyl)-2-propanone

Figure 6. ^{13}C NMR spectrum of the products of the MIM-catalyzed reaction of 4-methoxyphenylacetic acid with acetic anhydride: 4-methoxyphenyl-2-propanone and 1,3-bis(4-methoxyphenyl)-2-propanone

Figure 7. ¹³C NMR spectrum of the products of the MIM-catalyzed reaction of 2-phenylbutanoic acid with acetic anhydride: 3-phenyl-2-pentanone

Figure 8. ¹H NMR spectrum of the products of the MIM-catalyzed reaction of 2-phenylbutanoic acid with acetic anhydride: 3-phenyl-2-pentanone.

Figure 9. ^1H NMR spectrum of the reaction mixture of the MIM-catalyzed reaction of 4-nitrophenylacetic acid with acetic anhydride after five minutes.

Figure 10. ^1H NMR spectrum of the reaction mixture of the MIM-catalyzed reaction of 4-nitrophenylacetic acid with acetic anhydride after forty-eight hours

3- ^1H NMR kinetics for 1-benzylimidazole and 1-methylimidazole:

The relative concentrations of reactants and products in the reaction mixture were determined using the ^1H NMR peak areas of specific protons from each compound. The peaks monitored were all singlets. Chemical shifts were 3.75 ppm, 3.723 ppm, 3.721 ppm, 3.69 ppm and 3.63 ppm for phenylacetic acetic anhydride, 1,3-diphenyl-2-propanone, diphenylacetic anhydride, phenyl-2-propanone and phenylacetic acid, respectively (Figure 11 and 12).

Figure 11. The ¹H NMR spectra of the reaction mixture at different times during the 1-benzylimidazole-catalyzed reaction. Samples were removed from the reaction mixture at the times shown on each spectrum.

Figure 12. The ^1H NMR spectra of the reaction mixture at different times during the MIM-catalyzed reaction. Samples were removed from the reaction mixture at the times shown on each spectrum.

References

- (1) Hayes, J.; Shipman, M.; Twin, H. *J. Org. Chem.* **2002**, *67*, 935.
- (2) Dolhem, E.; Ocafrain, M.; Nedelec, J. Y.; Troupel, M. *Tetrahedron* **1997**, *53*, 17089.
- (3) L'Esperance, R.; Engen, D. V.; Dayal, R.; Pascal, R. *J. Org. Chem.* **1991**, *56*, 688.
- (4) Gallardo, I.; Guirado, G.; Marquet, J. *Eur. J. Org. Chem.* **2002**, *2*, 261.
- (5) Pecunioso, A.; Menicagli, R. *J. Org. Chem.* **1988**, *53*, 45.