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Metalation of α-diazocarbonyl compounds using Grignard reagents. A convenient synthesis of α-diazo-β-ketoesters and mixed esters of α-diazomalonate

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Abstract—α-Diazocarbonyl compounds react with methylmagnesium bromide at −78 °C generating the corresponding α-diazo-α-bromomagnesio species, which can be intercepted by various electrophilic reagents. For example, with alkyl chloroformates α-diazo-β-ketoesters or mixed esters of α-diazomalonate are obtained in good yields.

α-Diazo-β-ketoesters are of considerable importance as precursors of carbonyl ylides,[1] and recently have also been used to prepare furo[3,4-*c*]furan derivatives.[2]

In connection with a current synthetic study, we required an array of α-diazo-β-ketoesters in which the acyl portion of the molecule was widely varied. The diazo transfer reaction to β-ketoesters,[3] which is one of the most frequently used syntheses of these compounds, was inappropriate for our purposes because the required β-ketoesters were not readily accessible. The direct acylation of diazoacetic esters although attractive, is limited in scope to reactive acyl halides[4] and anhydrides (e.g., trifluoroacetic anhydride).[5] It is known that α-diazoacetic acid esters react with aldehydes and imines in the presence of NaOH[6] or DBU.[7] In addition, α-metalated diazo compounds based on lithium,[8] silver,[9] mercury,[10] or zinc[11] are easily generated and react with various electrophilic reagents. We attempted to adapt several of these methods to the synthesis of α-diazo-β-ketoesters from α-diazoketones and alkyl chloroformates, but they either failed completely, or were of limited generality. We were attracted by the report of Schöllkopf et al.[12] concerning the deprotonation of ethyl diazoacetate with methylmagnesium iodide and the subsequent generation of ethyl α-diazopropionate upon reaction of the α-iodomagnesio species with methyl iodide. This report describes the successful adaptation of this methodology to the synthesis of α-diazo-β-ketoesters from α-diazoketones and alkyl chloroformates.

In a model study, an equimolar amount of methylmagnesium bromide in THF was added to a THF solution of ethyl diazoacetate at −78 °C (inert atmosphere). After 30 min at −78 °C an equimolar amount of ethyl chloroformate was added and after an additional 30 min at −78 °C, the reaction was quenched with aqueous NH_4Cl. Column chromatographic purification on silica gel gave diethyl diazomalonate in 81% yield. Not only was this process readily applicable to the synthesis of mixed esters of α-diazomalonate (Table 1, entries 9–11), it could also be used to prepare α-diazo-β-ketoesters from α-diazoketones (entries 1–7).[13] Further-more, electrophilic reagents such as di-*tert*-butyldicarbonate, MEM chloride, *p*-toluenesulfonyl chloride, and piperonal produced the new α-diazo-β-substituted carbonyl compounds shown in entries 11–14.

This synthesis of functionalized α-diazocarbonyl compounds has one important limitation. Substrates with acidic hydrogens α to the carbonyl moiety are deprotonated at this site and the carbanionic species so produced cyclizes. For example, the diazoketone **1**[18] is converted into the enolate **2**, which on acidification gives

Keywords: Diazoketone; Grignard reagent; Diazoketoester; Diazomalonate.
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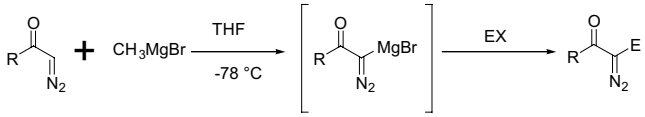
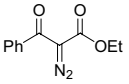
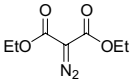
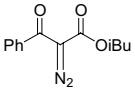
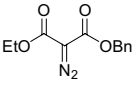
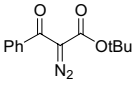
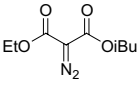
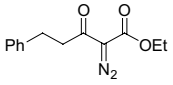
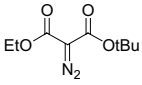
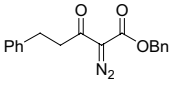
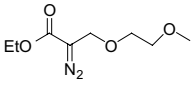
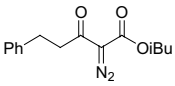
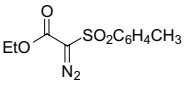
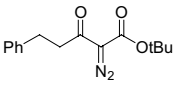
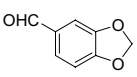
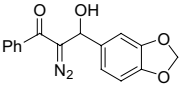
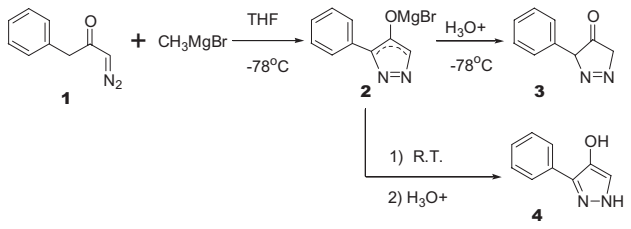
Table 1. Diazocompounds prepared from α-diazocarbonyl compounds, methylmagnesiumbromide and diverse electrophiles



Entry	R	Electrophile	Diazocompound	Yield (%)	Entry	R	Electrophile	Diazocompound	Yield (%)
1[14]	Ph	ClCOOEt		79	8[15]	EtO	ClCOOEt		81
2	Ph	ClCOO*i*-Bu		98	9[4d]	EtO	ClCOOBn		82
3	Ph	$(BOC)_2O$		68	10	EtO	ClCOO*i*-Bu		73
4	$PhCH_2CH_2$	ClCOOEt		58	11[16]	EtO	$(BOC)_2O$		63
5	$PhCH_2CH_2$	ClCOOBn		45	12	EtO	ClMEM		44
6	$PhCH_2CH_2$	ClCOO*i*-Bu		42	13[17]	EtO	$ClSO_2C_6H_4CH_3$		88
7	$PhCH_2CH_2$	$(BOC)_2O$		42	14	Ph			97

the very unstable, but spectroscopically characterizable pyrazolinone **3**.[19] If the enolate solution is left at room temperature (12 h), acidification gives crystalline 3-phenyl-4-hydroxypyrazole **4**[20] (75% yield). This route to 4-hydroxypyrazoles has ample literature precedent (Scheme 1).[21]

In summary, α-diazo-β-keto esters, mixed esters of α-diazomalonates, and other β-substituted α-diazocarbonyl compounds are easily prepared from α-diazo-α-bromomagnesio carbonyl compounds and the appropriate electrophilic reagent. The simplicity of the method suggests that this route to β-functionalized α-diazocarbonyl compounds will enjoy widespread application.



Scheme 1. Generation of pyrazolinone **3** and hydroxypyrazole **4** from **1**.

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13. Typical procedure for the synthesis of α-diazo-β-keto-esters. 3.0 M Ethereal MeMgBr (0.33 mL, 1 mmol) was added to a stirred solution of the diazoketone (1 mmol) in dry THF cooled to −78 °C (N_2 atmosphere). The requisite electrophilic reagent was then added neat at −78 °C and thereafter stirring was continued at this temperature for an additional 30 min. Saturated aqueous NH_4Cl (15 mL) was then added to the reaction mixture and the product was extracted with ether (3×10 mL). The extract was dried over Na_2SO_4, the solvent was removed in vacuo and the product was purified by column chromatography (SiO_2, hexane/AcOEt 9:1). Selected spectral data. Entry 2: IR ($CHCl_3$, cm^{-1}) 2962, 2091, 1713; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.96 (d, 6H), 1.91 (m, 1H), 3.85 (d, 2H), 7.09–7.70 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 19.3, 19.3, 27.0, 72.2, 74.6, 126.8, 126.8, 127.8, 127.8, 135.5, 136.1, 169.4, 183.2; MS [EI+] m/z (RI%): 246 $[M]^+$ (5), 105 $[Ph-CO]^+$ (100). Entry 3: IR ($CHCl_3$, cm^{-1}) 2984, 2110, 1720; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.52 (s, 9H), 7.09–7.70 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 29.1, 29.1, 29.1, 72.9, 75.3, 126.4, 126.4, 127.7, 127.7, 135.2, 136.0, 170.1, 183.1 MS [EI+] m/z (RI%): 246 $[M]^+$ (10), 105 $[Ph-CO]^+$ (100). Entry 4: IR ($CHCl_3$, cm^{-1}) 2982, 2089, 1762, 1709; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.33 (t, 3H), 3.77 (t, 2H), 3.61 (t, 2H), 4.29 (q, 2H), 6.97–7.33 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.3, 31.1, 41.5, 63.0, 74.9, 126.5, 126.5, 127.7, 127.7, 135.3, 136.4, 177.8, 212.5; MS [EI+] m/z (RI%): 246 $[M]^+$ (2), 91 $[PhCH_2$, $M-CH_2COCN_2CO_2Et]^+$ (100). Entry 5: IR ($CHCl_3$, cm^{-1}) 3029, 2092, 1716; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.99 (t, 2H), 3.39 (t, 2H), 5.11 (s, 2H), 6.97–7.33 (m, 10H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 31.1, 41.5, 67.1, 75.4, 126.1, 128.4, 128.4, 128.5, 130.4, 130.4,131.3, 131.3 135.2, 138.1, 177.1, 213.3; MS [EI+] m/z (RI%): 308 $[M]^+$ (5), 91 $[PhCH_2]^+$ (100). Entry 6: IR ($CHCl_3$, cm^{-1}) 2963, 2117, 1770; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.96 (d, 6H), 1.91 (m, 1H), 3.85 (d, 2H), 3.01 (t, 2H), 3.38 (t, 2H), 6.97–7.33 (m, 5 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 19.0, 19.0, 27.0, 31.1, 41.2, 72.2, 74.6, 126.1, 128.4, 128., 130.4, 130.4, 139.0, 177.1, 213.3; MS [EI+] m/z (RI%): 274 $[M]^+$ (10). Entry 7: IR ($CHCl_3$, cm^{-1}) 2951, 2103, 1739; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.51 (s, 9H), 3.66 (d, 2H), 2.95 (t, 2H), 6.97–7.33 (m, 5 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 29.1, 29.1, 29.1, 31.3, 42.0, 72.9, 75.3, 126.1, 128.4, 128.4, 130.4, 130.4, 139.0, 177.2, 213.3; MS [EI+] m/z (RI%): 274 $[M]^+$ (8), 91 $[PhCH_2]^+$ (100). Entry 10: IR ($CHCl_3$, cm^{-1}) 2964, 2141, 1713; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.94 (d, 6H),1.28 (t, 3H), 3.85 (d, 2H), 4.24 (q, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.3, 19.0, 19.0, 27.0, 72.2, 73.7, 74.6, 177.1, 177.9; MS [EI+] m/z (RI%): 214 $[M]^+$ (5), 0.73 $[CO_2CH_2CH_3]^+$ (100). Entry 12: IR ($CHCl_3$, cm^{-1}) 2975, 2141, 1713; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.33 (t, 3H), 3.40 (s, 3H); 3.57 (t, 2H), 3.72 (t, 2H), 4.24 (q, 2H); 4.76 (s, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.3, 58.5, 58.7, 68.2, 70.5, 72.8,171.4; MS [EI+] m/z (RI%): 202 $[M]^+$ (5), 0.29 $[CH_2CH_3]^+$ (100). Entry 14: p.f. 62 °C; IR ($CHCl_3$, cm^{-1}) 3360, 2909, 2090, 1686; ^1H NMR ($CDCl_3$, 200 MHz) δ 6.06 (s, 2H), 6.74 (s, 1H), 6.94 (d, 1H), 6.97–7.63 (m, 7H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 65.2, 69.7, 123.8, 123.8, 125.7, 125.7, 126.8, 126.8, 127.8, 127.8, 133.2, 135.4, 136.1, 139.7, 189.7; MS [EI+] m/z (RI%): 296 $[M]^+$ (5), 268 $[M-N_2]^+$ (5), 251 $[M-N_2-OH]^+$ (5), 151 $[M-CN_2COC_6H_5]^+$ (100).
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19. Preparation of compound **3**. A THF solution of the bromomagnesio derivative of the α-diazoketone **1** (1 mmol) was prepared as described above, and after 30 min at −78 °C saturated aqueous NH_4Cl (15 mL) was added to the reaction mixture. The product was extracted with ether (3×10 mL), the extract was dried over Na_2SO_4, and the solvent was removed in vacuo to give compound **3** as a very unstable, red oil (62%). Selected spectral data for compound **3**: ^1H NMR ($CDCl_3$, 300 MHz) δ 5.13 (s, 2H), 6.19 (s, 1H), 7.19–7.36 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 55.0, 68.0, 127.1, 128.7, 128.7, 129.2, 129.2, 134.3, 197.8; MS [EI+] m/z (RI%): 160 $[M]^+$ (25), 77 $[C_6H_5]^+$ (100); IR (film, cm^{-1}) 2108, 1732.
20. Preparation of compound **4**. A solution of the bromomagnesio derivative of **1** (1 mmol) was prepared as described above. After 30 min at −78 °C, the cooling bath was removed, and after 12 h at room temperature, the reaction mixture was worked up as described for the synthesis of **3** above. The crude product was purified by column chromatography (SiO_2, hexane/AcOEt 8:2) to afford a yellow solid (75%), mp 128–130 °C. Selected spectral data for compound **4**: ^1H NMR ($CDCl_3$, 300 MHz) δ 5.10 (br s, 1H), 7.12 (s, 1H), 7.23 (m, 1 H), 7.29 (m, 2H), 7.32 (m, 2H), 7.88 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 126.1, 127.6, 128.1, 128.1, 129.4, 129.4, 138.1, 140.6, 142.9; MS [EI+] m/z (RI%): 160 $[M]^+$ (30), 143 $[M]^+$ (50), 77 $[C_6H_5]^+$ (100); IR (film, cm^{-1}) 3321, 1650.
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