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# Ethyl 2-Diazomalonyl Chloride. An Efficient Diazoacylating Reagent

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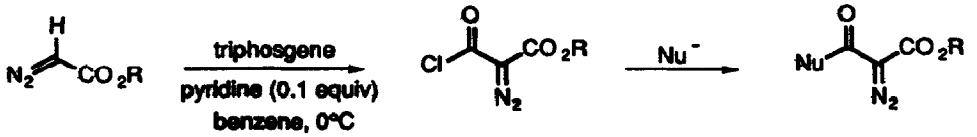
**Abstract:** Ethyl 2-diazomalonyl chloride readily reacts with aromatic and aliphatic amines, alcohols, thiols, and amides to form a variety of α-diazo carbonyl species.

α-Diazo carbonyl compounds have found numerous applications in organic synthesis, and their use in either heterocyclic or carbocyclic ring formation is well precedented.[1-8] The Arndt-Eistert sequence employs the Wolff rearrangement of an α-diazo ketone to a ketene in the one-carbon homologation of carboxylic acids.[9] Ring contraction of cyclic diazo ketones represents a general method for the preparation of highly strained small ring compounds.[10] α-Diazo carbonyl compounds are also precursors to metallo-carbenoid intermediates when exposed to many metal complexes or salts.[11] Typically, α-diazo carbonyl systems are constructed by diazo transfer to a methylene unit adjacent to one or more electron-withdrawing groups.[12] Occasionally, difficulties are encountered because the yield of product may be low, undesirable side reactions may compete with diazo transfer, or the lability of the diazo compound precludes its isolation.[13] In this communication we present an alternate and a very facile procedure which enables the one-pot preparation of a variety of α-diazo carbonyl compounds under mild conditions. This new route involves formation of the diazo compound by reaction of a nucleophilic reagent with ethyl 2-diazomalonyl chloride.




1; R=Et
2; R=$^t$Bu

3; R=Et
4; R=$^t$Bu

Ethyl 2-diazomalonyl chloride (3)[14] has attracted some previous attention from the biochemical community since it serves as a photoaffinity label in proteins and as an active site directed modifier of nucleophilic side chains of enzymes.[15] This compound is a pale yellow oil which is preparable in high yield from inexpensive starting materials and can be stored indefinitely at -20°C. By using the procedure described below, we have been successful in preparing large quantities (10–20 g) of 3 from

ethyl diazoacetate and triphosgene. The material is an exceptionally safe diazoacetylating agent[16] as we have been unable to initiate a detonation by friction, shock or rapid heating. A related experimental protocol was used to prepare *t*-butyl 2-diazomalonyl chloride (**4**) starting from *t*-butyl diazoacetate[17] and triphosgene.

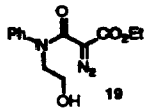
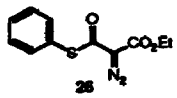
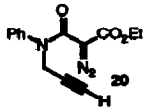
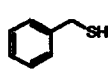
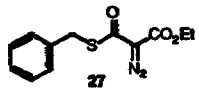
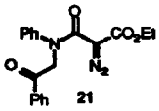
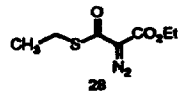
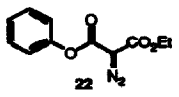
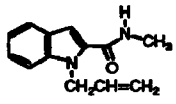
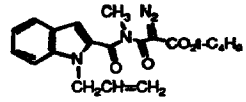
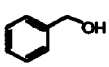
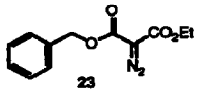
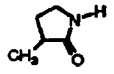
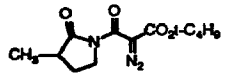
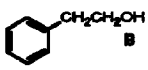
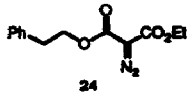
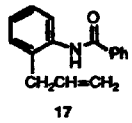
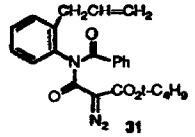
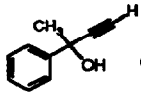
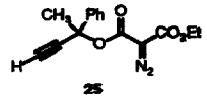
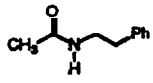
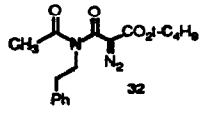
As can be seen in Table I, diazoacetamides are readily produced in good-excellent yield by the rapid diazoacetylation of amines under neutral conditions. Reactions were typically complete within 1 h at 0°C. This represents a significant improvement over previous syntheses of acid-sensitive diazoacetyl compounds and can be advantageously compared to the previously reported methods of diazoacetylation.[16] Both reagents **3** and **4** react with alcohols, thiols and amides under neutral or basic conditions. Selective N-diazoacetylation occurred using a 1,2-amino alcohol. The utilization of **3** with alcohols results in the formation of diazo ketoesters in high yield (Table I). Diazoacetylation of phenol (entry 4) as well as benzylic or aliphatic alcohols (entries 5 and 6) is extremely efficient under basic conditions (2,6-lutidine or NaH). Even a hindered alcohol such as **11** (*i.e.*, entry 7) could be acylated with this reagent in good yield. Our method also lends itself to the efficient preparation of diazo thioesters. Thus, aromatic or aliphatic thiols were readily converted to diazo thioesters (entries 8-10) under several different reaction conditions producing the desired products in good yield.

Entries 11-14 demonstrate the applicability of the method to the preparation of diazo amidoesters. It was necessary to use the lithium salt (*i.e.*, n-BuLi + $R_1CONHR_2$) in order for reaction to occur. Unactivated amides do not react with diazomalonyl chloride **3**. These examples represent the first case where a diazoacetylating agent has been used to prepare a diazoimide directly from an amide. Diazoacetamidation classically involves two steps, one of which consists of a diazo transfer reaction.[18] Although most of the reactions examined employ the ethyl ester **3**, the t-butyl reagent **4** exhibited similar selectivity. In all cases, the product was easily separated from by-products on chromatography over silica gel (EtOAc/hexane).

***Experimental Procedure***

*Preparation of Ethyl 2-Diazomalonyl Chloride (**3**). To a 3-necked flask equipped with a cold finger and thermometer is added 16.8 g (56.6 mmol) of triphosgene and 75 mL of benzene. The mixture is cooled to 0°C and 0.5 g (6.0 mmol) of pyridine is added resulting in the formation of a white precipitate. To this solution is added 16.1 g (0.14 mol) of ethyl diazoacetate at such a rate so that the internal temperature did not rise above 10°C The mixture is warmed to 25°C and stirred for 4-6 h. The red solution was filtered through a pad of celite, concentrated under reduced pressure and distilled (bp 60-62°C (1.5 mm)) to give 11.0 g (44%) of **3** as a yellow liquid; IR (neat) 2120 $cm^{-1}$; $^{13}C$-NMR ($CDCl_3$, 75 MHz) δ 14.1, 62.7, 64.1, 153.4, and 158.4.*

**TABLE 1**

| entry | nucleophile | method | yield | product | entry | nucleophile | method | yield | product |
|---|---|---|---|---|---|---|---|---|---|
| 1 | PhNHCH$_2$CH$_2$OH **5** | A | 66% |  **19** | 8 |  **12** | B<br>C | 91%<br>76% |  **26** |
| 2 | PhNHCH$_2$C≡CH **6** | A | 76% |  **20** | 9 |  **13** | B<br>C | 78%<br>59% |  **27** |
| 3 | PhNHCH$_2$COPh **7** | A | 65% |  **21** | 10 | CH$_3$CH$_2$SH **14** | B | 75% |  **28** |
| 4 |  **8** | B | 93% |  **22** | 11 |  **15** | D | 73% |  **29** |
| 5 |  **9** | B | 92% |  **23** | 12 |  **16** | D | 66% |  **30** |
| 6 |  **10** | B | 96% |  **24** | 13 |  **17** | D | 60% |  **31** |
| 7 |  **11** | C | 73% |  **25** | 14 |  **18** | D | 57% |  **32** |

**Method A:** Diazomalonyl chloride **3** (1.0 equiv), THF, 0°C.
**Method B:** Diazomalonyl chloride **3** (1.5 equiv), 2,6-lutidine (2.0 equiv), $CH_2Cl_2$, 0°C.
**Method C:** (1) NaH, THF, 0°C; (2) Diazomalonyl chloride **3** (1.1 equiv).
**Method D:** (1) n-BuLi (1.2 equiv), THF, -78°C; (2) Diazomalonyl chloride **4** (1.5 equiv).

*Typical Procedure for Diazoacetylation*

***Method A.*** *To a solution of the amine in THF at 0°C was added reagent **3** (1 equiv). Standard aqueous workup, drying over $Na_2SO_4$, evaporation of the solvent under reduced pressure and purification by silica gel chromatography gave the purified product.*

***Method B.*** *To a solution of the amine or thiol and 2,6-lutidine (2.0 equiv) in $CH_2Cl_2$ at 0°C, was added reagent **3** (1.5 equiv). Standard workup as above gave the purified product.*

***Method C.*** *To a suspension of NaH (1.5 equiv) in THF at 0°C was added a solution of the alcohol or thiol in THF. Reagent **3** (1.5 equiv) was added and the mixture was warmed to 25°C. Standard workup as above gave the purified product.*

***Method D.*** *To a solution of the amide in THF at -78°C was added a solution of n-BuLi in hexane.*

*To this mixture was added reagent 4 (1.5 equiv) and the mixture was warmed to 25°C. Standard workup as above gave the purified product.*[19]

In summary, diazoacetylation using ethyl 2-diazomalonyl chloride provides a convenient method for the preparation of a variety of diazo carbonyl compounds. Further applications of diazoacetylating agents 3 and 4 are being investigated in our laboratory.

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**References and Notes**

1. Burke, S. D.; Grieco, P. A. *Org. React.* **1979**, *26*, 361.
2. Doyle, M. P. *Acc. Chem. Res.* **1986**, *19*, 348.
3. Maas, G. *Topics in Current Chemistry* **1987**, *137*, 77.
4. Wulfman, D. S.; Poling, B. In *Reactive Intermediates*; Abramovitch, R. A., Ed.; Plenum: New York, 1980; Vol. 1, p. 321.
5. Moody, C. J.; Pearson, C.; Lawton, G. *Tetrahedron Lett.* **1985**, 3171.
6. Hudlicky, T.; Reddy, D. B.; Govindan, S. V.; Kulp, T.; Still, B.; Sheth, J. P. *J. Org. Chem.* **1983**, *48*, 3422.
7. Wenkert, E.; Alonso, M. E.; Buckwaler, B. L.; Sanchez, E. L. *J. Am. Chem. Soc.* **1983**, *105*, 2021.
8. Taber, D. F.; Petty, E. H. *J. Org. Chem.* **1982**, *47*, 4808. Taber, D. F.; Petty, E. H.; Raman, K. *J. Am. Chem. Soc.* **1985**, *107*, 196.
9. Regitz, M.; Maas, G. *Diazo Compounds: Properties and Synthesis;* Academic Press: Orlando, FL, 1986; p. 185. Ando, W. In "*The Chemistry of the Diazonium and Diazo Groups*"; Patai, S., Ed.; Wiley: New York; 1978, Part 1, p. 458.
10. Redmore, D.; Gutsche, C. D. *Adv. Alicyclic Chem.* **1971**, *3*, 125-136.
11. Padwa, A.; Hornbuckle, S. F. *Chem. Rev.* **1991**, *91*, 263. Padwa, A.; Krumpe, K. E. *Tetrahedron* **1992**, *48*, 5385.
12. Regitz, M. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 733. Taber, D. F.; Ruckle, R. E.; Hennessy, M. J. *J. Org. Chem.* **1986**, *51*, 4077.
13. Danheiser, R. L.; Miller, R. F.; Brisbois, R. G.; Park, S. Z. *J. Org. Chem.* **1990**, *55*, 1959.
14. Weygand, F.; Bestmann, H. J.; Fritzsche, H. *Chem. Ber.* **1960**, *93*, 2340.
15. Vaughn, R. J.; Westheimer, F. H. *Anal. Biochem.* **1969**, *29*, 305. Brunswick, D. J.; Cooperman, B. S. *Proc. Nat. Acad. Sci. USA* **1971**, *68*, 1801. Kline, T. B.; Nelson, D. L.; Namboodiri, K. *J. Med. Chem.* **1990**, *33*, 950. Wender, P. A.; Irie, K.; Miller, B. *J. Org. Chem.* **1993**, *58*, 4179.
16. For the use of other diazoacylating reagents, see: Onihia, A.; Rene, L.; Guilhem, J.; Pascard, C.; Badet, B. *J. Org. Chem.* **1993**, *58*, 1641. Corey, E. J.; Myers, A. G. *Tetrahedron Lett.* **1984**, *25*, 3559. Bestmann, H. J.; Soliman, F. M. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 947. Ok, H.; Caldwell, C.; Schroeder, D. R.; Singh, A. K.; Nakanishi, K. *Tetrahedron Lett.* **1988**, *29*, 2275. Zimmerman, H. E.; Bunce, R. A. *J. Org. Chem.* **1982**, *47*, 3377. Rogers, J. D.; Caldwell, G. W.; Gauthier, A. D. *Tetrahedron Lett.* **1992**, *33*, 3272.
17. Ledon, H. J. in *Organic Synthesis;* Wiley: New York, 1988; Coll. Vol. VI, p. 414.
18. Doyle, M. P.; Pieters, R. J.; Tannton, J.; Pho, H. Q.; Padwa, A.; Hertzog, D. L.; Precedo, L. *J. Org. Chem.* **1991**, *56*, 820.
19. All new compounds were completely characterized (IR; $^{1}$H-NMR, $^{13}$C-NMR and analytical data). Yields reported in Table I correspond to isolated products.

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