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This Week's Citation Classic®

Schlenk H & Gellerman J L. Esterification of fatty acids with diazomethane on a small scale. *Anal. Chem.* **32**:1412-14, 1960.
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Esterification by diazomethane is adapted to milligram scale, minimizing the noxious features of the reagent. The reaction is instantaneous when CH_2N_2 with N_2 as carrier gas is bubbled into the solution of fatty acids in diethyl ethermethanol, 10:1. The procedure is well-suited for esterification with $^{14}CH_2N_2$. [The *SCI*® indicates that this paper has been cited in over 860 publications since 1960.]

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Diazomethane had to be prepared by the senior author (H.S.) when he was a student in an organic chemistry lab course. Pechmann had described CH_2N_2 40 years before that time,[1,2] and the possibility that its use in esterification might become the topic of an often-quoted publication would appear remote. Pechmann already had reported the methylation of acids and recommended this reaction for preparation of their esters on a small scale. Also, the serious adverse health effects that he suffered from CH_2N_2 were described. Luckily, he did not experience any explosions that, with H_2 as carrier gas (N_2 was not as readily available), might have been quite disastrous.

One can assume widespread use of the esterification method by the time it became a student item,[3,4] and familiarity with it could be taken for granted. Justifiably, such esterification is usually not referenced in the literature.

The survival of our publication as a *Citation Classic* may be due to procedural merits, such as expediency, small scale, and a simple apparatus. These outweigh the drawbacks of diazomethane. Instability in storage, potential explosion (*Organic Syntheses* describes or refers to the necessary precautions in preparing CH_2N_2 in each of its several versions), and short- and long-term toxicity[5] do not invite its routine use. These negative aspects also apply to some of the precursors that can cause undesirable methylation. (See references 6 and 7 for reviews of this subject.)

At the time of our publication, gas chromatography and other microanalytical methods had matured and afforded many more precise analyses of fatty acid mixtures than ever practical before. In most of these techniques, the fatty acids preferably were, and still are, in the form of methyl esters, and this required a facile method for esterification of many acid samples.

To meet this need, we modified the time-honored esterification method into an expedient procedure and explored the conditions for rapid and complete reaction. It is safe not only for autoxidizable fatty acids but also for the investigator. Diazomethane can explode for many reasons, but one can work safely with it when appropriate precautions are maintained. The small scale gives additional assurance, but not certainty, against hazard, and it should not lead to negligence.

A bonus of our procedure is the ease of esterification with $^{14}CH_2N_2$ that is inherent in the small scale. Open transfer of the volatile reagent is avoided, which minimizes loss and radioactive contamination. In many instances, the publication may have been cited for this particular application.

Were the procedure to be novel today, we would describe it as we did 25 years ago, adding only that we have used it routinely without incident or bad effects. We would still feel that it deserves publication in its own right rather than as an abstract-style paragraph buried in another context. In view of shifts in topics and readership, we might now send the manuscript to one of the newer journals devoted to lipids where fatty acid methyl esters are a mainstay in research.

1. **Pechmann H V.** Ueber Diazomethan. *Ber. Deut. Chem. Ges.* **27**:1888-91. 1894.
2. ----------. Ueber Diazomethan (2. Mittheilung.). *Ber. Deut. Chem. Ges.* **28**:855-61. 1895.
3. **Gattermann L & Wieland H.** *Die Praxis des Organischen Chemikers.* Berlin: De Gruyter. 1925. 379 p.
4. **Beilstein F K.** *Handbuch der organischen chemie.* Hamburg: Voss. 1881. Vol. I. p. 318.
5. **Gutsche C D.** The reaction of diazomethane and its derivatives with aldehydes and ketones. *Organic Reactions* **8**:364-429. 1954.
6. **Hart R W, Hall K Y & Daniel F B.** DNA repair and mutagenesis in mammalian cells. *Photochem. Photobiol.* **28**:131-55. 1978.
7. **Singer B.** N-nitroso alkylating agents: formation and persistence of alkyl derivatives in mammalian nucleic acids as contributing factors in carcinogenesis. *J. Nat. Cancer Inst.* **62**:1329-38. 1979. (Cited 180 times.)