

This Week's Citation Classic®

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Stork G, Brizzolara A, Landesman H, Szmuszkowicz J & Terrell R. The enamine alkylation and acylation of carbonyl compounds.

J. Amer. Chem. Soc. 85:207-22, 1963.

[Chandler Laboratories, Columbia University, New York, NY]

This is a comprehensive paper that put together our work on the enamine alkylation, a new method demonstrating that monoalkylation of ketones and aldehydes could be achieved via reaction of the derived enamines with electrophilic carbon species. [The *SCI*® indicates that this paper has been cited in over 945 publications.]

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It is hard to realize today that, although the carbonyl group had long been recognized as the preeminent function in organic synthesis, there was by the mid-1940s no method available for the alkylation of aldehydes. The monoalkylation of ketones could be achieved, but only by previous conversion to a β -ketoester, alkylation, and decarboxylation.

I had often thought that there must be milder ways of accomplishing such transformations, and I imagined that, perhaps, the enamine tautomers of some sort of imine derived from the condensation of a carbonyl group and an amino acid might be involved in some biochemical alkylations. These musings, which owed much to my biochemical naiveté, eventually led me to wonder if enamines, whether biologically relevant or not, might undergo alkylation on carbon. The evidence was discouraging. In the 20 years or so that enamines of ketones and aldehydes had been known, there had only been scattered reports of "normal" alkylation on the nitrogen atom.

This was the state of affairs when, a few months after I moved to Columbia in October 1953, luck intervened in the form of Ross Terrell, a graduate student who was doing a thesis with Layton McCoy, then an instructor. Ross had been attempting to monomethylate a ketone, specifically 5-phthalimido-2-tetralone. As everyone who has worked with 2-tetralones will appreciate, monomethylation was—and still is—essentially unattainable via the usual metal enolates; mixtures containing mostly dimethylated products arise. I suggested to Terrell that he find out what would happen if he were to treat the pyrrolidine enamine from his ketone with methyl iodide. This was an extremely lucky first case, for although yields were only moderate at first, they soon reached around 80 percent. This is a typical yield with 2-tetralones, but is decidedly higher than can be obtained from the *methylation* of most ketone enamines.¹ Without this remarkable result, we might not have gone on to discover the general alkylation of all types of enamines with electrophilic olefins (with Hans Landesman²) or the acylation reaction of ketone enamines (with A. Brizzolara, Jr.).

I have, of course, derived much satisfaction from the fact that while no reference to the carbon alkylation of enamines (other than to our own work) could be found either in the 1954 or in the 1955 *Chemical Abstracts* index, the index for the first half of 1985 (volume 102) not only has an entry for "enamines" in the Chemical Subjects index, but also has at least 40 references to reactions of specific enamines with carbon electrophiles.

In some ways, I am surprised, but pleased, that the 1963 enamine paper is still being quoted as much as it is, even though there are now excellent comprehensive summaries of the chemistry of this fascinating class of substances.³⁻⁶

1. Stork G, Terrell R & Szmuszkowicz J. A new synthesis of 2-alkyl and 2-acyl ketones. *J. Amer. Chem. Soc.* 76:2029-30, 1954. (Cited 195 times since 1955.)
2. Stork G & Landesman H K. A new alkylation of carbonyl compounds. II. *J. Amer. Chem. Soc.* 78:5128-9, 1956. (Cited 90 times.)
3. Cook A G. *Enamines*. New York: Marcel Dekker, 1969. 515 p. (Cited 385 times.)
4. Hickmott P W. Enamines: recent advances in synthetic, spectroscopic, mechanistic, and stereochemical aspects—I. *Tetrahedron* 38:1975-2050, 1982.
5. -----, Enamines: recent advances in synthetic, spectroscopic, mechanistic, and stereochemical aspects—II. *Tetrahedron* 38:3363-446, 1982.
6. -----, Recent advances in the chemistry of conjugated enamines. *Tetrahedron* 40:2989-3051, 1984.