Fundamental Concept?" The article focused on the "ambiguous limitations of non-peptide solid-phase chemistry whose resolution is required if the process is to mature from publishable novelty to fundamental methodology."[70] By the mid-1980s, however, advances in polymer science, automation, and chemical synthesis paved the way for explosive growth in the field of high throughput synthesis, beginning with the independent work of Richard Houghten[71] and H. Mario Geysen.[72] Houghten and Geysen separately described methods for the synthesis of large arrays of small peptides using solid support and successfully applied them to identify biologically active peptides. The practice of high throughput chemistry transitioned out of peptides and into druglike space by the early 1990s with the nearly simultaneous disclosure of the synthesis of arrays of functionalized 1,4-benzodiazepines on solid support by Jonathan A. Ellman[73] and S. Hobbs DeWitt (Figure 2.15).[74]

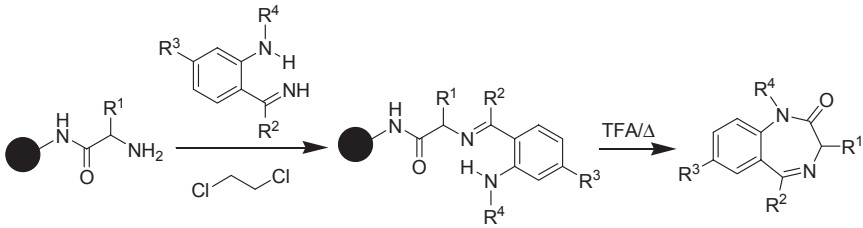

FIGURE 2.15 In 1992, professor Jonathan Ellman and his colleagues demonstrated that 1,4-benzodiazepine derivatives could be prepared on solid support. The application of solid phase chemistry to produce analogs of market drugs such as Valium® (diazepam), Ativan® (lorazepam), and Rivotril® (clonazepam) demonstrated that drug-like compounds could be prepared in this manner.

After these seminal reports, pharmaceutical companies began to incorporate the concepts and practices of solid phase synthesis and high throughput chemistry into their research programs. Resin-bound synthesis continued to progress into the small molecule arena,[75] but at the same time, older techniques were reexamined and new technologies were developed with the goal of increasing the synthetic output of medicinal chemists. Multicomponent reactions designed to incorporate multiple elements of diversity in a single step, such as the Ugi reaction,[76] the Biginelli reaction,[77] and the Passerini reaction[78] were revisited and employed to generate libraries of druglike compounds (Figure 2.16). New equipment dedicated to the rapid synthesis of hundreds, if not thousands, of compounds was developed, along with the technology necessary to purify, store, and retrieve hundreds of thousands of compounds. By the end of the twentieth century, compound collections at most major pharmaceutical companies had eclipsed 500,000 compounds,[65] and by 2013, the number of commercially available screening compounds exceeded 21 million.[79]