A NEW APPROACH TO 6-NITRO-1H-[1,4]-DIAZEPINES

Nagatoshi Nishiwaki,* Takuma Ogihara, Mina Tamura, Noriko Asaka, Kazushige Hori, Yasuo Tohda, and Masahiro Ariga*

Department of Chemistry, Osaka Kyoiku University, Asahigaoka 4-698-1, Kashiwara, Osaka 582-8582, Japan

Abstract - 2,3-Disubstituted 2,3-dihydro-6-nitro-1H-[1,4]-diazepines are prepared with easy experimental manipulations from formylated nitroenamine, which behaves as the synthetic equivalent of nitromalonaldehyde usable in organic media.

Nitro compounds constitute an important class among organic compounds, and numerous preparative methods have been developed.¹ Nitration is a powerful method to introduce a nitro group, but it often suffers from restrictions such as severe conditions, limited scope of substrates and regioselectivity. As another approach, the building block having a nitro group is employed for construction of nitro compounds those are hardly prepared by alternative procedure. Nitromalonaldehyde (NMA), one of useful synthons, is so unstable that its sodium salt (Na-NMA) has been widely used from old time² despite some problems to be settled. Preparation of Na-NMA accompanies somewhat troublesome manipulations,³ and reactions using Na-NMA are conducted in only aqueous media because of insolubility into general organic solvents. Furthermore, Na-NMA before purification should be treated as explosive material. Thus, it is highly desired to develop a convenient and safe synthetic equivalent of NMA in the synthetic chemistry of nitro compounds.

In our course of study on functionalized nitroenamine chemistry,⁴ we established an easy preparative method for formylated nitroenamine (1).⁴c Nitroenamine (1) possessing two electrophilic sites is considered to behave as the synthetic equivalent of NMA usable in organic media. In the present work, 2,3-dihydro-6-nitro-1H-[1,4]diazepine⁵,⁶ is focused as a new target system, which is important skeleton for drug design.

Only a few reports dealing with 5,7-diphenyl- and 5,7-dimethyl-6-nitrodi azepines are found,⁶a,b however, the system having a substituent at the 2- or 3-positions is not known except for a single description of 2,2-dimethyl derivative.⁶c We would like to show here a new preparative method for the title compounds.
When 1,2-diaminoethane (2a) was added to a solution of nitroenamine (1) in methanol, white precipitates were immediately generated. After the mixture was stirred at room temperature for 3 h, white precipitates were filtered off [product (3a), yield 31 %, based on 1], and then the filtrate was concentrated to afford white solid [product (4a), yield 69 %]. Both products (3a) and (4a) give the same empirical formula with elemental analysis, but these are obviously different compounds from a viewpoint of solubility. Product (4a) is determined as nitrodiazepine with X-Ray crystallography in addition to spectral and analytical data. On the other hand, low solubility of 3a into organic solvents prevents the recrystallization and the structural analysis, however, it is considered to be an oligomer (probably dimer). Quantitative synthesis of diazepine (4a) is realized with slowly adding a solution of 2a to a solution of nitroenamine (1) to avoid oligomerization.

The present reaction is applicable to sterically hindered diamines (2b-e). Reactions of nitroenamine (1) with N-ethylated diamine (2b) or 1,2-diaminopropane (2c) similarly afford corresponding diazepines (4b) and (4c) in good yields, respectively. When 1,2-diaminocyclohexanes (2d) and (2e) are used, the condensation effectively undergoes leading to bicyclic diazepines (4d) and (4e) fused in cis- and trans-mode.

In the case of 1,2-diaminobenzene (2f), different reactivity is observed. In the MS spectrum of reddish solid precipitated during the reaction, a parent peak for dimeric structure (3f) is observed, but the peak for
benzodiazepine (4f) is not detected. Although larger oligomer might be formed as by-products, the major content is surely dimer (3f), and we have obtained no evidence for the presence of diazepine (4f). In this case, dilution of the reaction mixture is not effective and also affords dimer 3f. In the old references, some descriptions about 4f are found and are quite similar to the data of 3f prepared by us. This means the product in the literature might not have a diazepine structure. It is considered that the lack of flexibility of 2f cannot form a seven membered ring. At any rate, dimer (3f) is readily prepared in a quantitative yield in our reaction. In consideration of the recent spotlight on β-diketiminate ligand, this reaction is also useful for preparation of tetradebate ligand \(^\text{10}\) having nitro groups.\(^\text{11}\)

In summary, we present a novel procedure for synthesis of nitrodiazepines (4a-e) and macrocyclic compound (3f) with considerably simple manipulations, namely, only mixing reagents at room temperature followed by the filtration of products. Furthermore, easily treatable nitroenamine (1) can be used as the synthetic equivalent of NMA with safety.

REFERENCES AND NOTES
7 Spectral data for 4a. Colorless granules; mp 194-195 °C (decomp); IR (KBr / cm\(^{-1}\)) 1571, 1344; \(^1\)H NMR (400 MHz, DMSO-\(d_6\), TMS) \(\delta\) 3.65 (s, 4H), 8.50 (s, 2H), 9.3-9.6 (br, 1H); \(^13\)C NMR (100 MHz,
DMSO-\textsubscript{d\textsubscript{6}}, TMS) $\delta$ 50.8 (t), 122.0 (s), 151.2 (d); MS (FAB) 142 (M$^+$+1, 100). Anal. Calcd for C\textsubscript{5}H\textsubscript{7}N\textsubscript{3}O\textsubscript{2}: C, 42.55; H, 5.00; N, 29.77. Found: C, 42.80; H, 5.05; N, 29.67. **Crystal data for 4a:** $M = 141.13$, orthorhombic, space group P2\textsubscript{1}2\textsubscript{1}2\textsubscript{1}. $a = 8.192(2)$ Å, $b = 11.5000(9)$ Å, $c = 6.674(1)$ Å, $V = 628.7(2)$ Å$^3$, $D = 1.491$ g/cm$^3$, $Z = 4$, F(000) = 296.00, $\mu = 1.18$ cm$^{-1}$. A pale yellow crystal of dimensions 0.20 x 0.20 x 0.40 mm was mounted at a glass fiber and used for measurement at 293 K on a Rigaku AFC7R four-circle diffractometer employing graphite monochromated MoK$\alpha$ radiation ($\lambda = 0.71069$ Å) using the $\omega/2\theta$ scan technique. The 2519 unique reflections were corrected for Lorentz and polarization effects. The structure was solved by direct methods (SAPI91). The final full-matrix least squares refinement, based on $F$ using 707 reflections ($I > 3.00\sigma(I)$) and 197 parameters, converged with $R = 0.036$ and $R_w = 0.026$.


