

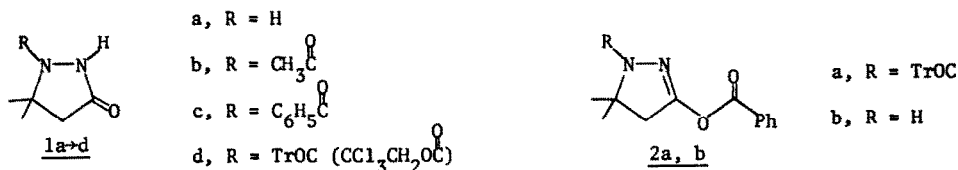
A NOVEL ACYL EXCHANGE REACTION IN THE SYNTHESIS OF 2-ACYL-PYRAZOLIDIN-3-ONES

Charles E. Hatch and Peter Y. Johnson*

Department of Chemistry, The Johns Hopkins University
Baltimore, Maryland 21218 U.S.A.

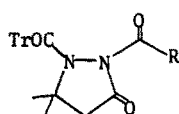
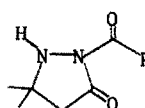
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As part of our synthetic work leading to the photolyses of pyrazolidin-3-ones, we found it necessary to synthesize a variety of previously unreported 1-acyl and 2-acyl-5,5-dimethylpyrazolidin-3-ones. While the 1-acetyl, 1b (mp 141-142°), and 1-benzoyl, 1c (mp 236-237°), isomers could be prepared from the parent heterocycle, 1a,¹ by reacting it with triethylamine and the appropriate acyl chloride in THF, attempts to make the 2-benzoyl isomer from the anion of 1a or via cyclization of 3,3-dimethylacrylic acid (or its ethyl ester) with benzoyl hydrazine gave no isolatable 2-acyl derivatives. Treatment of 1-(2,2,2-trichloroethoxycarbonyl²)-5,5-dimethylpyrazolidin-3-one, 1d (mp 210-211°) (prepared analogously to 1b), with benzoyl chloride and triethylamine for 6 hrs at 25° in THF gave, after filtration of hydrochloride salts and evaporation of the THF, a white solid. Purification of this crude product, simply by washing it with cold ether, gave analytically pure 2a in 70% yield (mp 124-125°). This O-benzoylated compound rearranged to give the N-benzoylated isomer 3a (mp 182-183°) when heated at 140° for 90 min.³ While 2a (a mixed anhydride) was readily hydrolyzed by aqueous base to 1d, 3a (an imide) was stable under similar conditions. These results support the isomer assignments of these two compounds.



Treatment of 3a with zinc in acetic acid gave, after work-up, the desired 2-benzoyl isomer 4a (mp 112-113°) in 63% yield. However, treatment of 2a under similar conditions did not give the expected mixed anhydride 2b, or its N-isomer 4a, but rather gave the 2-acetyl isomer 4b (mp 67-68°) in 60 to 70% yield. This novel acyl exchange reaction was found to be general. Reaction of 2a with zinc and propionic, isobutyric or pivalic (50% in THF) acid gave products 4c, 4d, and 4e respectively. The yields of these products were found to decrease slightly as the apparent size of the exchanging acid increased. In a typical example of these acyl exchange reactions, the starting

material was dissolved in a minimum amount of glacial acetic acid and four equivs. of zinc dust were added. After allowing the mixture to stir for 2 hrs under nitrogen, it was poured into cold aqueous potassium carbonate and the water layer was extracted with chloroform. Drying and subsequent removal of the chloroform gave the crude product which was purified by recrystallization. Treatment of 2a under conditions which might result in O to N isomerization or acyl transfer (i.e. stirring in acetic acid, or in acetic acid with $ZnCl_2$), but which would not be expected to remove the protecting group, either failed to give reaction or resulted in hydrolysis of the benzoyl group to give 1d. It is believed that steric and electronic factors related to the protecting group prevent substitution on the nitrogen at the 2-position unless stringent, nonhydrolytic conditions are used. For example, 3b could be obtained from 2a in 70% yield by refluxing 2a in acetic anhydride for 6 hrs. The lack of rearrangement (with or without exchange) while TrOC remains on the molecules, under conditions

3a, ba, R = C_6H_5 b, R = CH_3 4a-ea, R = C_6H_5 b, R = CH_3 c, R = C_2H_5

d, R = i-Pr

e, R = t-Bu

equivalent (except for the zinc metal) to those of the TrOC removal reactions, leads us to postulate 2b as an intermediate in these reactions which subsequently reacts to give the observed products. Work on the mechanism of this rearrangement is in progress.

The novel acyl exchange-rearrangement occurring during the removal of the protecting group from the O-acyl isomers provides a synthetic approach to N-acyl derivatives in this and possibly related systems. Full spectra and analyses are in agreement with proposed structures.

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References

1. H. Dorn and D. Arndt, J. Prakt. Chem., 313 (1), 115 (1971).
2. Abbreviated as TrOC; see T. B. Windholtz and D. B. R. Johnson, Tetrahedron Lett., 2555 (1967).
3. For other examples of this type of rearrangement see D. Y. Curtin and J. H. Engelmann, J. Org. Chem., 37, 3439 (1972).