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Direct Conversion of α-Halo Acids into α-Halo Amides by Reaction with 2-Phenylazirine

David St.C. Black and James E. Doyle

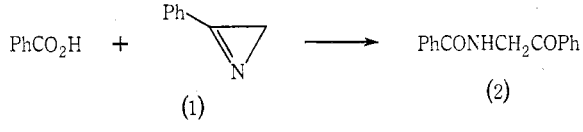
Department of Chemistry, Monash University, Clayton, Vic. 3168.

Abstract

Chloro-, bromo-, iodo- and cyano-acetic acids undergo reaction with 2-phenylazirine to afford the highly crystalline 2-chloro-, 2-bromo-, 2-iodo- and 2-cyano-*N*-phenacylacetamides respectively.

Introduction

Various nucleophiles add[1] with ease to the imine carbon atom of 2-phenylazirine (1)[2] to produce, initially at least, a substituted aziridine containing a nucleophilic nitrogen atom. Thus, 2-phenylazirine (1) shows interesting bifunctional reactivity. In particular, the reaction of benzoic acid with compound (1) has been reported[3] to yield *N*-phenacylbenzamide (2) (Scheme 1).



(1) (2)

Scheme 1

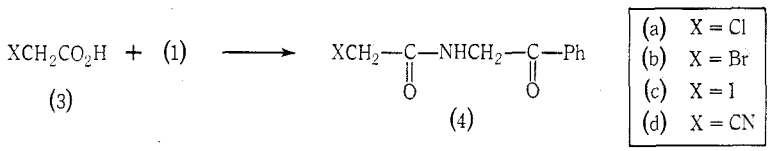
In view of this apparently very mild method of obtaining an amide from a carboxylic acid, it was of interest to investigate the reaction of compound (1) with more sensitive carboxylic acids and in particular those containing an additional electrophilic site. A range of α-halo acids was chosen.

Results and Discussion

Chloroacetic acid (3a) reacted readily with compound (1) to yield 2-chloro-*N*-phenacylacetamide (4a). Replacement of the chloro group by bromo, iodo or cyano did not change the type of reaction but afforded the products (4b–d) respectively (Scheme 2). The structures of (4a) and (4b) were confirmed by comparison of their spectroscopic data with those of authentic samples. The new compounds (4c) and

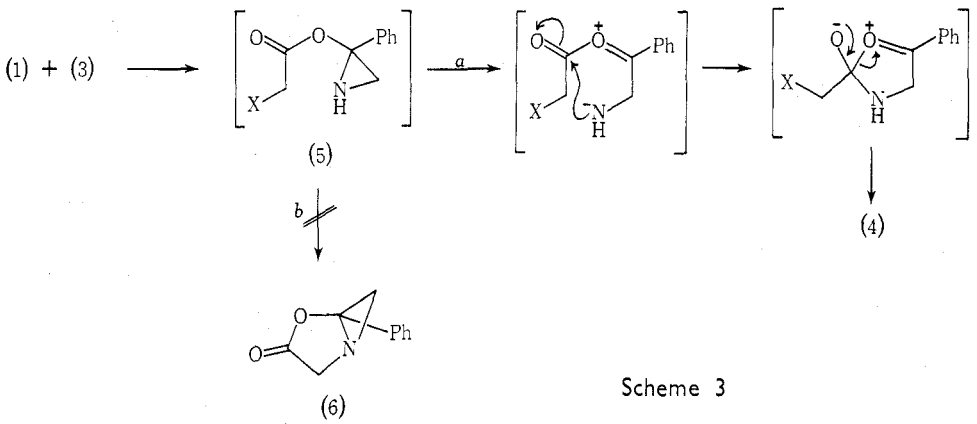
[1] Fowler, F. W., *Adv. Heterocycl. Chem.*, 1971, **13**, 45.
[2] Hortmann, A. G., Robertson, D. A., and Gillard, B. K., *J. Org. Chem.*, 1972, **37**, 322.
[3] Sato, S., Kato, H., and Ohta, M., *Bull. Chem. Soc. Jpn*, 1967, **40**, 2938.

(4d) were formulated on the basis of their elementary analyses and spectroscopic properties.



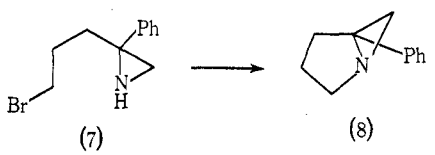
Scheme 2

The amides (4) were formed quite cleanly and isolated pure in yields of 40–66%. These yields have not been maximized and are probably relatively low because of the small scale of reactions. These amides (4) thus provide readily accessible crystalline derivatives of the acids (3).



Scheme 3

A possible route to the formation of the amides (4) is shown in Scheme 3, path *a*. The instability of the proposed aziridine intermediate (5) is presumably caused by the 2-acyloxy substituent and the mechanistic path *a* would also be consistent with the formation of the amide (2) from benzoic acid. However, in the absence of such instability cyclization of (5) by neighbouring group displacement to the bicyclic compound (6) (path *b*) would be a possibility. Indeed, the azabicyclohexane (8) has been formed[4] by cyclization of the aziridine (7) (Scheme 4).



Scheme 4

None of the bicyclic compound (6) was detected in the reactions of the acids (3) with 2-phenylazirine (1), which behaves as a masked amino ketone nucleophile showing clear selectivity for addition to a carboxyl derivative in preference to substitution of an alkyl halide. Such masked nucleophilic behaviour could have other uses.

[4] Chaabouni, R., Laurent, A., and Marquet, B., *Tetrahedron Lett.*, 1976, 3149.

Experimental

Melting points are uncorrected. Microanalyses were performed by the Australian Microanalytical Service, Melbourne. Infrared spectra were recorded on a Perkin–Elmer 257 grating infrared spectrometer and refer to paraffin mulls. ^{1}H n.m.r. spectra were measured at 60 MHz with a Varian A56/60 spectrometer and refer to solutions in deuterochloroform with tetramethylsilane as internal reference. Spectra are reported in the following order: chemical shift measured in ppm downfield from tetramethylsilane (δ), multiplicity, coupling constant, assignment. Signals caused by protons of NH groups were identified by exchange with D_2O.

2-Chloro-N-*phenacylacetamide* (*4a*)

2-Phenylazirine[2] (1) (1·0 g, 8·5 mmol) was dissolved in dry benzene (20 ml), chloroacetic acid (3a) (810 mg, 8·5 mmol) was added and the solution was heated under gentle reflux for 2 h. The reaction mixture was heated to dryness and the residual brown solid (1·34 g) was continuously extracted with hexane to give 2-chloro-*N*-phenacylacetamide (4a) (900 mg, 50%) which was recrystallized from benzene/n-hexane, m.p. 123–124° (lit.[5] 118°). This material was identified by comparison of the infrared and ^{1}H n.m.r. spectra with those of an authentic sample prepared by heating phenacylamine hydrochloride[6] with chloroacetyl chloride in dry benzene.

2-Bromo-N-*phenacylacetamide* (*4b*)

2-Phenylazirine[2] (1) (585 mg, 5 mmol) was dissolved in dry benzene, bromoacetic acid (3b) (695 mg, 5 mmol) was added and the solution was heated under reflux for 1 h. The solution was filtered hot and the 2-bromo-*N*-phenacylacetamide (4b) which precipitated was recrystallized from benzene, (500 mg, 40%), m.p. 148–149° (lit.[7] 147–149°). The acetamide was identified by comparison of its spectroscopic characteristics with those of an authentic sample prepared by heating phenacylamine hydrochloride[6] with bromoacetyl bromide in benzene.

2-Iodo-N-*phenacylacetamide* (*4c*)

2-Phenylazirine[2] (1) (585 mg, 5 mmol) was dissolved in dry benzene (20 ml), iodoacetic acid (3c) (925 mg, 5 mmol) was added and the solution was heated under reflux for 1·5 h. The solid left after removal of the solvent was recrystallized from benzene to give *2-iodo*-N-*phenacylacetamide* (4c) (1·0 g, 66%) as golden platelets, m.p. 162–162·5° (Found: C, 39·8; H, 3·4. $C_{10}H_{10}INO_2$ requires C, 39·6; H, 3·3%). ν_{max} 3240s, 3040w, 1687m, 1660m, 1630s, 1598w, 1585w, 1550m, 1380m, 1315w, 1285w, 1240s, 1185s, 1035w, 1000w, 775s, 705s cm^{-1}. N.m.r. spectrum (δ): 3·82, s, ICH_2; 4·8, d, *J* 4 Hz, NCH_2CO; 7·2–8·1, m, (NH and phenyl protons).

2-Cyano-N-*phenacylacetamide* (*4d*)

2-Phenylazirine[2] (1) (585 mg, 5 mmol) was dissolved in dry benzene (20 ml), cyanoacetic acid (3d) (425 mg, 5 mmol) was added and the solution was heated under reflux for 1·5 h. The hot solution was filtered and allowed to cool. The *2-cyano*-N-*phenacylacetamide* (4d) which precipitated was collected and recrystallized from benzene (400 mg, 42%), m.p. 160–161° (dec.) (Found: C, 64·9; H, 5·1. $C_{11}H_{10}N_2O_2$ requires C, 65·3; H, 5·0%). ν_{max} 3300s, 2260w, 1680m, 1660s, 1640m, 1600m, 1560m, 1400m, 1370m, 1235m, 1200w, 760m cm^{-1}. N.m.r. spectrum (δ): 3·52, s, $NCCH_2$; 4·83, d, *J* 4 Hz, NCH_2CO; 7·2–8·1, m, NH and phenyl protons.

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[6] Baumgarten, H. E., and Petersen, J. M., *J. Am. Chem. Soc.*, 1960, **82**, 459.
[7] Shvaika, O. P., and Klimisha, G. P., *Khim. Geterotsikl. Soedin.*, 1966, 677 (*Chem. Abstr.*, 1967, **66**, 46356m).