Organic & Biomolecular Chemistry

RSC Publishing

PAPER

View Article Online
View Journal | View Issue

Remarkable effect of CF_3CH_2OH for the halogen induced oxidative rearrangement reaction of aminals leading to 3,4-dihydroquinazolines†

Cite this: *Org. Biomol. Chem.*, 2013, **11**, 2648

Received 22nd January 2013,
Accepted 8th February 2013

DOI: 10.1039/c3ob40132d

www.rsc.org/obc

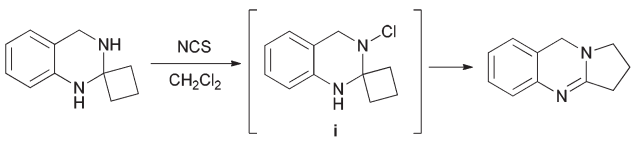
Kenichi Murai, Masato Shimura, Ryu Nagao, Daisuke Endo and Hiromichi Fujioka*

CF_3CH_2OH was found to be a useful solvent for the oxidative rearrangement reactions of aminals promoted by *N*-chlorosuccinimide, which proceed *via* the intermediacy of *in situ* formed chloro-aminals and that produce 3,4-dihydroquinazolines.

The fluorine containing alcohols, 2,2,2-trifluoroethanol (CF_3CH_2OH) and 1,1,1,3,3,3-hexafluoroisopropanol ($(CF_3)_2CHOH$), have attracted much attention in modern organic synthesis. These alcohols have unique properties that include high polarity, low nucleophilicity, high hydrogen bonding donor strength, low hydrogen bonding acceptor strength, and high ionizing power. Owing to these properties, fluorous alcohols remarkably enhance reactivity and, as a result, they have been used as solvents for a variety of reactions.[1–3]

We recently described a novel rearrangement reaction of spirocyclic cyclobutane aminals that are derived from *o*-aminobenzyl amine and cyclobutanones (Scheme 1).[4] In this process, 3,4-dihydroquinazoline derivatives are produced *via* a pathway that involves *in situ* formation of the corresponding chloroamines (*e.g.*, **i**), generated by treatment of the substrates with *N*-chlorosuccinimide (NCS). In contrast to the related rearrangement reaction of simple chloro-amines, which require activation by silver salts,[5] transformations of *o*-aminobenzyl amine and cyclobutanone derived chloro-aminals proceed *via* spontaneous ring expansion reactions *via* a C-to-N migration mechanism. The electron donating ability of the neighboring non-chlorinated nitrogen in the aminal moiety significantly assists the ring expansion process. Although this reaction serves as a new method for 3,4-dihydroquinazoline synthesis, it is limited to starting aminals that contain cyclobutane structures where the release of ring strain is an important driving force.[6]

In the investigation described below, we uncovered a remarkable accelerating effect of a fluorous alcohol on the rearrangement reactions of chloro-aminals. Importantly, the use of CF_3CH_2OH as the solvent for these processes removes the previously described substrate limitation and, consequently, the reaction now represents a general methodology for the preparation of a variety 3,4-dihydroquinazoline derivatives.[7]



Scheme 1 Previously described ring strain induced rearrangement reactions of cyclobutanone derived aminals.

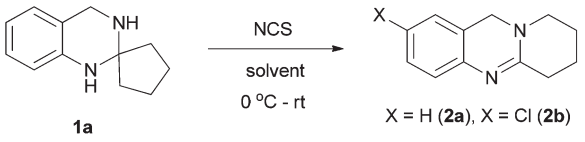
Our initial investigation of the effect of solvents on the rearrangement reactions of *N*-chloro-aminals focused on aminal **1a**, prepared from *o*-aminobenzylamine and cyclopentanone. In contrast to observations made in our earlier studies with cyclobutanone aminals, we observed that treatment of **1a** with NCS in CH_2Cl_2 does not promote formation of the desired rearrangement product **2a** (Table 1, entry 1). Similar observations were made when **1a** was treated with NCS in other solvents, such as toluene, THF, and CH_3CN. Even when EtOH was used as the solvent, the reaction produced only a trace amount of the desired product that is detected by using TLC (entries 2–5). In contrast, we found that **1a** reacts with NCS in CF_3CH_2OH to generate the desired rearrangement product **2a** in 45% yield (entry 6). Interestingly, use of the more polar fluorinated alcohol, $(CF_3)_2CHOH$, results in a process that generates only a low yield of the desired product along with a complex mixture of other substances (entry 7).

The drastic effect of CF_3CH_2OH in promoting the rearrangement of the reaction of the *N*-chloro-derivative of **1a** is interesting. Although, to the best of our knowledge, there is no report on the reaction of halo-amines and *N*-chloro-aminals in CF_3CH_2OH, we postulate that the observed efficiency

Graduate School of Pharmaceutical Sciences, Osaka University, 1-6 Yamada-oka, Suita, Osaka 565-0871, Japan. E-mail: fujioka@phs.osaka-u.ac.jp; Fax: +81 6 6879 8229; Tel: +81 6 6879 8226

†Electronic supplementary information (ESI) available. See DOI: 10.1039/c3ob40132d

Table 1 Optimization[a]

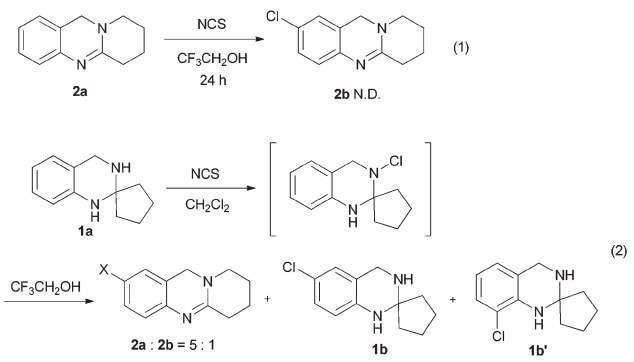


Entry	Solvent	Time	Yield (%) (**2a** : **2b**)[b,c]
1	CH_2Cl_2	24 h	N.D.[d]
2	Toluene	24 h	N.D.[d]
3	THF	24 h	N.D.[d]
4	CH_3CN	24 h	N.D.[d]
5	EtOH	24 h	Trace
6	CF_3CH_2OH	24 h	54 (5 : 1)
7	$(CF_3)_2CHOH$	24 h	35 (1 : 1)
8	CF_3CH_2OH (0.02 M)	24 h	82 (7 : 1)

[a] Unless otherwise noted, reactions were carried out on a 0.1 M solution of **1a** with 1.1 eq. of NCS. [b] Combined yields. [c] Ratios were determined by using ^{1}H NMR analysis of crude reaction mixtures. [d] N.D. = not detected.

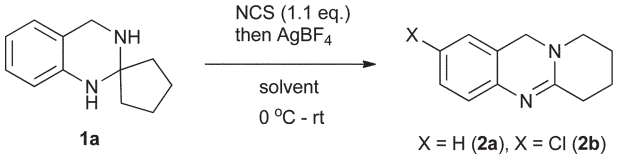
enhancement is a consequence of the highly polar and low nucleophilic properties of this fluorinated alcohol, which could aid in facilitating the N–Cl bond cleavage reaction that promotes rearrangement.

Further studies were carried out to optimize the yields of the aminal ring expansion reaction.[8] To determine if the only moderate yield of **2a** of the reaction of **1a** with NCS is a consequence of competitive chlorination of the aromatic rings in the starting aminal and/or 3,4-dihydroquinazoline product, control experiments were performed (Scheme 2). The results of the first experiment show that the reaction of **2a** with NCS in CF_3CH_2OH (eqn (1)) does not give chlorinated product **2b**. Secondly, we observed that the reaction of **1a** with NCS in CH_2Cl_2 produces the chloro-aminal intermediate and no aromatic ring chlorinated product (judged by TLC). Addition of CF_3CH_2OH (in the same volume as CH_2Cl_2 (total 0.1 M)) to the above reaction mixture leads to formation of the rearrangement product **2a** along with its chlorinated analog **2b**, and chlorinated aminals **1b** and **1b′** (eqn (2)).[9] These observations suggest that the initial chloro-aminal formed in CH_2Cl_2 likely acts as the reagent for aromatic ring chlorination taking place in CF_3CH_2OH. Thus, it is plausible to consider that CF_3CH_2OH



Scheme 2 The results of control experiments.

Table 2 Reactions using $AgBF_4$



Entry	Solvent	$AgBF_4$	Yield[a] (**2a** + **2b**)	**2a** : **2b**[b]
1	Toluene (0.1 M)	1.1 eq.	N.D.	—
2	CH_2Cl_2 (0.1 M)	1.1 eq.	22%	—[c]
3	CH_2Cl_2 (0.1 M)	3.0 eq.	29%	3 : 1
4	CF_3CH_2OH (0.02 M)	1.1 eq.	68%	2 : 1

[a] Combined yield. [b] Ratios were determined by using ^{1}H NMR analysis of crude reaction mixtures. [c] Only **2a** was obtained.

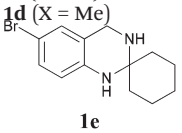
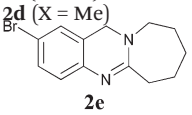
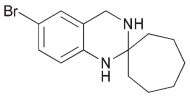
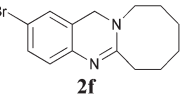
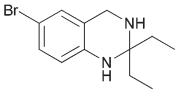
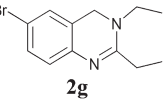
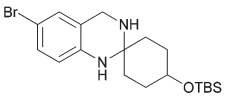
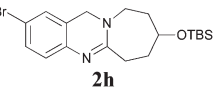
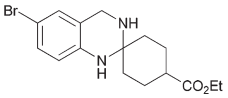
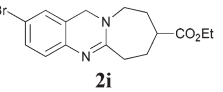
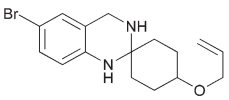
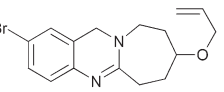
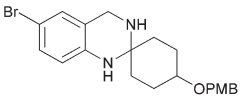
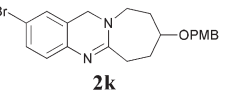
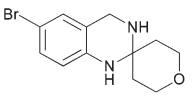
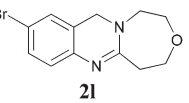
enhances the N–Cl bond cleavage reaction and that this enhancement is responsible for both the intramolecular rearrangement and intermolecular aromatic ring chlorination reactions. This reasoning suggests that the efficiencies of the undesired intermolecular chlorination reactions would decrease when the process is conducted using dilute solutions. Indeed, we observed that the yield of **2a** increases to 82% when a dilute solution of **1a** (0.02 M) is subjected to the NCS promoted reaction in CF_3CH_2OH (Table 1, entry 8).

Owing to their reported use for activation of chloroamines,[5] the effects of silver salts, such as $AgBF_4$, on the yield of the rearrangement reaction of **1a** were investigated (Table 2). Although $AgBF_4$ did not promote the reaction when toluene was employed as the solvent (entry 1), it was found that the reaction of **1a** with NCS in CH_2Cl_2 followed by the addition of either 1.1 or 3.0 equivalents of $AgBF_4$ to the resulting solution results in production of the rearrangement product **2a** but in low yield (entries 2 and 3). In addition, the use of a combination of CF_3CH_2OH as the solvent and $AgBF_4$ as the activator does not improve the efficiency or the selectivity (**2a** : **2b** = 2 : 1) of the process (entry 4) over that observed when $AgBF_4$ is not utilized (Table 1, entry 8).

The substrate scope of the rearrangement reaction, carried out using NCS in CF_3CH_2OH, was explored (Table 3).[10,11] The results show that reactions of cyclopentanone derived aminals **1b–d**, derived from cyclopentanone and aromatic ring substituted (*e.g.*, Cl, Br, and Me) *o*-aminobenzyl amine, proceed in good yields (entries 2–4). Moreover, aminals prepared from cyclohexanone and cycloheptanone as well as the acyclic ketone, 3-pentanone, undergo the rearrangement reaction (entries 5–7). Furthermore, the presence of various functional groups, such as TBS ethers, esters, olefins, and *p*-methoxybenzyl ether does not significantly alter the efficiency of the reaction (entries 8–11). However, aminal **1l** containing a tetrahydropyran ring reacts to generate the rearrangement product in a low yield (entry 12), probably because of the electron withdrawing nature of the ether oxygen and its effect on the migration ability of carbon.[12]

In conclusion, the studies described above have led to the development of a general method for promoting oxidative

Table 3 Generality[a]

Entry	Aminal	Product	Yield[b]
1	**1a** (X = H)	**2a** (X = H)	71%
2	**1b** (X = Cl)	**2b** (X = Cl)	76%
3	**1c** (X = Br)	**2c** (X = Br)	79%
4	**1d** (X = Me)	**2d** (X = Me)	86%
5	 **1e**	 **2e**	73%
6	 **1f**	 **2f**	72%
7	 **1g**	 **2g**	69%
8	 **1h**	 **2h**	65%
9	 **1i**	 **2i**	61%
10	 **1j**	 **2j**	66%
11	 **1k**	 **2k**	62%
12	 **1l**	 **2l**	25%

[a] Conditions: **1** (1 eq.), NCS (1.1 eq.), CF_3CH_2OH (0.02 M), 0 °C–rt. [b] Isolated yield.

rearrangement reactions of aminals that generate 3,4-dihydroquinazolines. Observations made in this effort show that CF_3CH_2OH is an ideal solvent for this process owing to its enhancement effect on rearrangement reactions of chloro-aminal intermediates formed by the reaction with NCS. To the best of our knowledge, reactions of halo-amines as well as chloro-aminals in CF_3CH_2OH have not been described previously. Thus, it is possible that the effects of CF_3CH_2OH observed in this investigation are applicable to other transformations of halo-amines,[13] a question that is being pursued in further studies in our laboratory.

Experimental section

General procedure for preparation of aminal

3′,4′-Dihydro-1′*H*-spiro[cyclopentane-1,2′-quinazoline] (1a). *o*-Aminobenzylamine (**3a**) (273.0 mg, 2.23 mmol) and ketone **2** (1.0 or 1.2 eq.) was dissolved in $CHCl_3$ (0.2 M) and the reaction mixture was stirred for 1 day at 60 °C. The resulting solution was cooled to rt and evaporated *in vacuo* to give aminal **1a** as a yellow solid. Mp: 48 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.00 (ddd, J = 7.5, 7.5, 1.5 Hz, 1H), 6.92 (dd, J = 7.5, 1.5 Hz, 1H), 6.66 (ddd, J = 7.5, 7.5, 1.2 Hz, 1H), 6.48 (dd, J = 7.5, 1.2 Hz, 1H), 4.01 (s, 2H), 1.87–1.66 ppm (m, 8H); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 143.0, 127.1, 126.0, 120.5, 117.3, 114.9, 76.0, 43.3, 39.7(2C), 23.7(2C) ppm; IR (KBr): 3296, 2955, 1607, 1416, 1193 cm^{-1}; HRMS (EI): calcd for $C_{12}H_{16}N_2$ [M]: 188.1313, found 188.1325.

General procedure for oxidative rearrangement of aminal

7,8,9,11-Tetrahydro-6*H*-pyrido[2,1-*b*]quinazoline (2a).[14] To the solution of aminal **1a** (41.9 mg, 0.223 mmol) in CF_3CH_2OH (11.0 mL) was added NCS (32.8 mg, 0.246 mmol) at 0 °C and the mixture was stirred for 30 min. The resulting solution was allowed to warm to rt and stirred for 1 day. The reaction was quenched with sat. $Na_2S_2O_3$ aq. and CF_3CH_2OH was evaporated *in vacuo*. To the residue was added 0.5 *N* NaOH aq. followed by extraction with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and evaporated *in vacuo*. The residue was purified by column chromatography (AcOEt–MeOH–triethylamine = 20/2/1) to give amidine **2a** as a red oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.13 (ddd, J = 8.4, 8.4, 2.4 Hz, 1H), 7.05–6.98 (m, 2H), 6.71 (d, J = 8.4 Hz, 1H), 4.53 (s, 2H), 3.54 (t, J = 6.0 Hz, 2H), 2.59 (t, J = 6.8 Hz 2H), 2.02–1.94 (m, 2H), 1.83–1.74 ppm (m, 2H).

Acknowledgements

This work was financially supported by a Grant-in-Aid for Scientific Research (B) and for Young Scientists (B) from JSPS.

Notes and references

1 For reviews, see: (*a*) L. Eberson, M. P. Hartshorn, O. Persson and F. Radner, *Chem. Commun.*, 1996, 2105; (*b*) J.-P. Bégué, D. Bonnet-Delpon and B. Crousse, *Synlett*, 2004, 18; (*c*) I. A. Shuklov, N. V. Dubrovina and A. Börner, *Synthesis*, 2007, 2925; (*d*) T. Dohi, N. Yamaoka and Y. Kita, *Tetrahedron*, 2010, **66**, 5775.

2 For recent examples, see: (*a*) D. Petruzziello, A. Gualandi, S. Grilli and P. G. Cozzi, *Eur. J. Org. Chem.*, 2012, 6697; (*b*) S. Picon, M. Rawling, M. Campbell and N. C. O. Tomkinson, *Org. Lett.*, 2012, **14**, 6250; (*c*) P. Trillo, A. Baeza and C. Nájera, *J. Org. Chem.*, 2012, **77**, 7344; (*d*) H. Hinou, K. Hyugaji, F. Garcia-Martin, S. Nishimura and F. Albericio, *RSC Adv.*, 2012, **2**, 2729.

3 Our recent studies, see: (*a*) H. Fujioka, H. Komatsu, A. Miyoshi, K. Murai and Y. Kita, *Tetrahedron Lett.*, 2011, **52**, 973; (*b*) H. Fujioka, H. Komatsu, T. Nakamura, A. Miyoshi, K. Hata, J. Ganesh, K. Murai and Y. Kita, *Chem. Commun.*, 2010, **46**, 4133.
4 K. Murai, H. Komatsu, R. Nagao and H. Fujioka, *Org. Lett.*, 2012, **14**, 772.
5 (*a*) F. M. Schell and A. M. Smith, *Tetrahedron Lett.*, 1983, **24**, 1883; (*b*) F. M. Schell and R. N. Ganguly, *J. Org. Chem.*, 1980, **45**, 4069; (*c*) P. G. Gassman and A. Carrasquillo, *Tetrahedron Lett.*, 1971, **12**, 109; (*d*) P. G. Gassman, *Acc. Chem. Res.*, 1970, **3**, 26.
6 T. Seiser, T. Saget, D. N. Tran and N. Cramer, *Angew. Chem., Int. Ed.*, 2011, **50**, 7740.
7 For reviews on 3,4-dihydroquinazoline derivatives and related alkaloids, see: (*a*) D. J. Connolly, D. Cusack, T. P. O'Sullivan and P. J. Guiry, *Tetrahedron*, 2005, **61**, 10153; (*b*) S. B. Mhaske and N. P. Argade, *Tetrahedron*, 2006, **62**, 9787; (*c*) A. Witt and J. Bergman, *Curr. Org. Chem.*, 2003, **7**, 659.
8 Several chlorinating reagents, such as *t*BuOCl, NaOCl, 1,3-dichloro-5,5-dimethylhydantoin (DCDMH), 1,3,5-trichloroisocyanuric acid, were tested but the yields of **2a** were not improved. When the reactions were performed with NBS, the brominations of the aromatic rings of the aminals were observed predominantly both in CH_2Cl_2 and CF_3CH_2OH.
9 The ratio of **2a** : **2b** : **1b** : **1b′** is 15 : 3 : 4 : 3 (determined by crude ^{1}H NMR analysis).
10 Aminals used in this study are readily prepared by condensation reactions of the corresponding diamines and ketones.
11 The reaction with the aminal prepared from cyclopentanone and aliphatic diamine, such as 1,2-diphenyl ethylenediamine, under the conditions gave a complex mixture.
12 Chlorination on the aromatic ring of **1l** is mainly observed.
13 Recently, intermolecular reactions using the chloro amine as the electrophilic nitrogen source have been intensively studied, see: (*a*) T. J. Barker and E. R. Jarvo, *J. Am. Chem. Soc.*, 2009, **131**, 15598; (*b*) T. Kawano, K. Hirano, T. Satoh and M. Miura, *J. Am. Chem. Soc.*, 2010, **132**, 6900; (*c*) B. Shen, D. M. Makley and J. N. Johnston, *Nature*, 2010, **465**, 1027; (*d*) T. J. Barker and E. R. Jarvo, *Angew. Chem., Int. Ed.*, 2011, **50**, 8325; (*e*) T. Hatakeyama, Y. Yoshimoto, S. Ghorai and M. Nakamura, *Org. Lett.*, 2010, **12**, 1516; (*f*) D. M. S. Schietroma, M. R. Monaco, V. Bucalossi, P. E. Walter, P. Gentili and M. Bella, *Org. Biomol. Chem.*, 2012, **10**, 4692.
14 J. S. Fitzgerald, S. R. Johns, J. A. Lamberton and A. H. Redcliffe, *Aust. J. Chem.*, 1966, **19**, 151.