Dehydration of formamides using the Burgess Reagent: a new route to isocyanides

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1 PERKIN COMMUNICATION

The Burgess Reagent readily converts formamides into isocyanides in high yields and is particularly effective for substrates containing halide sensitive trimethylsilyl ether groups.

Introduction

Isocyanides **2** are versatile compounds which participate in a

R-NHCHO (**1**) R-NC (**2**) $Et_3\overset{+}{N}$-S(O)$_2$-$\overset{-}{N}CO_2Me$ (**3**)

a R = Cyclohexyl,
b R = Phenyl,
c R = Octyl,
d R = Cyclohex-1-enyl,
e R = Oleyl,
f R = Bu^tOCOCH_2—,

range of synthetically important transformations.[1] These reactions form the basis for new routes to heterocycles and for further developments in multi-component condensations, in particular.[2] Although isocyanides can be prepared from a variety of precursors,[3] dehydration of formamides is the most popular route but remains an experimentally non-trivial problem. We have applied the Burgess Reagent **3**,[4] to this functional group interconversion and much to our satisfaction, report that the reagent is highly effective for the preparation of a range of isocyanides from *N*-formylamines. This is a new application of **3** as a dehydrating agent in the area of organic nitrogen chemistry and the first α-elimination involving the reagent.

Our interest in reagent **3** developed from a problem encountered in the dehydration of β-trialkylsilyloxyformamides.[5] Substantial desilylation occurred with conventional halide based systems, particularly with trimethylsilyloxyformamides as substrates. A few halide-free reagents are known to convert formamides into isocyanides.[6] The Burgess Reagent is halide-free also. It is well established as a dehydrating agent for alcohols[7a–d] and is the reagent of choice for cyclo-dehydration reactions of amide derivatives.[8] Compound **3** also promotes the formation of nitriles and nitrile oxides from carboxamides and nitroalkanes respectively,[9] but to our knowledge has not been employed in the synthesis of isocyanides.

Results and discussion

Our initial experiments, with cyclohexylformamide **1a** as substrate, revealed that the isocyanide **2a** could be obtained in high yield by stirring a solution of the amide (1–3 mmol) with 1.1 to 2.0 equiv. of the dehydrating agent, in dry CH_2Cl_2 for 12 h at room temperature, followed by bulb to bulb distillation of the residue under vacuum. These conditions were suitable for several substrates (Table 1; entries 2 and 3) but chromatographic methods were required for the isolation and purification of the majority of isocyanides generated in our investigation.

We believe that many formamide dehydrations can be executed at room temperature by stirring a CH_2Cl_2 solution of the substrate with a slight excess (1.1 mmol per mmol substrate) of freshly prepared or recrystallized reagent **3**, but since the compound is moisture sensitive and has a limited shelf-life, use of a greater excess (at least 1.5 equiv.) is recommended for general use. Addition of extra reagent may be necessary for less reactive formamides and heating at reflux may be advantageous in certain cases. Wipf's polymer-based version of the Burgess Reagent[8g] may offer some additional practical improvements but we have not carried out any isocyanide syntheses using this compound.

Cyclohex-1-enylformamide **1d** gave the vinyl isocyanide **2d**, in good yield following dry-flash chromatography of the reaction residue on silica gel-60 with hexane as eluent (Table 1, entry 4). Similarly, oleylformamide [(*Z*)-undec-9-enyl] **1e**, as a mixture of geometrical isomers (from a commercially available mixture of *E*- and *Z*-oleylamine), produced **2e** in 69% yield (entry 5).

The glycine derivative **1f** was less reactive than **1a**–**e** under the conditions described above, but could be converted into **2f** using a higher excess of **3** (entry 6). Dehydration of the hindered formamide **4** was also problematic and a disappointing yield was obtained initially. Heating a solution of **4** at reflux proved to be a major improvement, however (entry 8). Interaction of the dipeptide **6** with the Burgess Reagent produced an optically active product **7** {mp = 62–64 °C, $[a]_D^{20}$ −13.8 (*c* = 1.0, $CHCl_3$}† and reaction at reflux was beneficial in terms of the yield and reaction time (entry 10).

In a key application of **3**, dehydration of **8**, derived from L-valinol, produced the labile isocyanide **9**, without loss of the $SiMe_3$ (TMS) group—the corresponding reaction with TsCl–pyridine resulted in a poor (39%) conversion to **9**. Likewise, the cyclohexyl derivative **12** could be converted into **13** in 61% yield (entry 14).

Interestingly, reaction of the formamido alcohol **10** with **3** in acetone (compound **10** is insoluble in CH_2Cl_2) displayed excellent selectivity and gave the novel hydroxy isocyanide **11** in high yield following reaction at room temperature or at reflux. No urethane or 2-oxazoline products, resulting from competing reactions of **10** with the reagent, were isolated following chromatography of the crude reaction product mixture on silica gel.

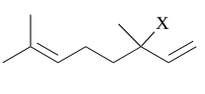
Extension of the chemistry to involve 3α-formamidocholestane **14** was successful and product **15** was obtained in a good yield which was improved further by conducting the reaction (0.37 mmol scale) at reflux in CH_2Cl_2 for 0.5 h. Acetoxyformamide **16**, obtained by sequential formylation (2 equiv. 4-nitrophenyl formate, CH_2Cl_2, 0 °C, 76%) and acetylation (Ac_2O, Py, 0 °C, 94%) of the requisite amino alcohol[10] was considered to be a more challenging substrate for the Burgess Reagent. Exposure of **16** (0.27 mmol scale) to two equivalents of reagent **3** at room temperature, effected a smooth conversion into the

† $[a]_D$ values are given in units of 10^{-1} deg cm^2 g^{-1}.

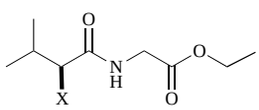
Table 1 Dehydration of formamides with the Burgess Reagent

Entry	Formamide	**3** (Equiv.)	*t*/h	Method[a]	Product	Yield (%)
1	**1a**	1.1	12	A	**2a**	89
2	**1b**	1.5	12	A	**2b**	91
3	**1c**	1.2	12	A	**2c**	82
4	**1d**	1.1	12	A	**2d**	77
5	**1e**	1.2	12	A	**2e**	69
6	**1f**	2.2	10	A	**2f**	78
7	**4**	2.0	24	A	**5**	38
8	**4**	1.5	1.3	B	**5**	88
9	**6**	1.5	12	A	**7**	70
10	**6**	1.5	1	B	**7**	80
11	**8**	2.0	2	A	**9**	70
12	**10**	1.1	12	C	**11**	78
13	**10**	1.1	0.5	D	**11**	77
14	**12**	2.0	1	A	**13**	61
15	**14**	1.4	12	A	**15**	64
16	**14**	1.5	0.5	B	**15**	82
17	**16**	2.0	12	A	**17**	82
18	**18**	2.0	36	A	**19**	46
19	**20**	2.0	12	A	**21**	32
20	**22**	1.5	36	A	**23**	84
21	**24**	2.0	12	A	**25**	84
22	**24**	1.5	1	B	**25**	72
23	**26**	3.0	36	A	**27**	71

[a] A: CH_2Cl_2 at room temperature; B: CH_2Cl_2 at reflux; C: acetone at room temperature; D: acetone at reflux.



4 X = NHCHO
5 X = NC



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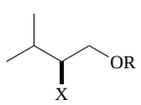
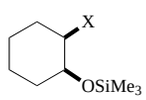
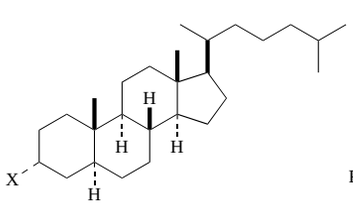
7 X = NC



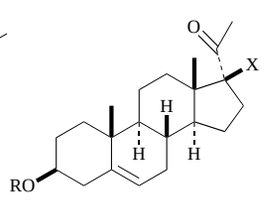
8 X = NHCHO, R = TMS
9 X = NC, R = TMS
10 X = NHCHO, R = H
11 X = NC, R = H



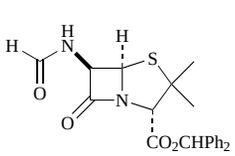
12 X = NHCHO
13 X = NC



14 X = NHCHO
15 X = NC



16 X = NHCHO, R = Ac
17 X = NC, R = Ac
18 X = NHCHO, R = H
19 X = NC, R = H



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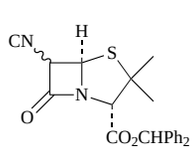

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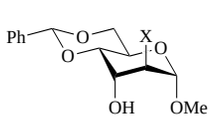
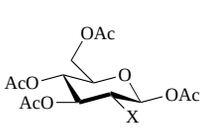


22 X = NHCHO
23 X = NC



24 X = NHCHO
25 X = NC

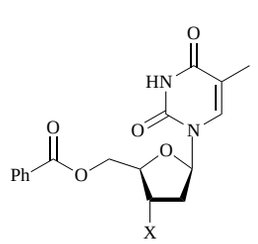
TMS = $SiMe_3$

isocyanide **17** (entry 17). Since the Burgess Reagent is known to dehydrate steroidal alcohols,[7a] the behaviour of alcohol **18** was of interest to us. The compound reacted slowly with **3** at room temperature (entry 18) and produced the novel hydroxy isocyanide **19** (mp 190–192 °C, ν_{max}/cm^{-1} 3430, 2160 and 1720) in modest yield, based on recovered starting material. Evidence for trace quantities of an olefinic product was seen in the 270 MHz ^{1}H NMR spectrum of the reaction product mixture but efforts to isolate the compound were unsuccessful.

Results with the β-lactam derivative **20** were also disappointing. Treatment of the compound with a total of four equivalents of Burgess Reagent, over a period of 48 h, gave a complex mixture from which no dehydration product could be isolated. Some conversion to the isocyanide could be achieved by reaction of **20** with an excess of **3** over a shorter period of time. Product **21** was isolated in poor yield (32%) as a mixture of C-6 epimers (α : β = 1 : 2).

Two amino sugar derivatives, **22** and **24** were included in our study. Formamide **22** was readily converted into the known[11] compound **23** (entry 20) without any evidence for a competing reaction at the unprotected secondary alcohol site also present in the structure. Dehydration of compound **24** was equally successful and gave the product **25** as a single anomer under two sets of conditions (entries 21 and 22).

Conclusion of the current phase of our investigation involved the formamidothymidine **26** as a substrate. The compound was obtained *via* azidolysis (NaN_3, DMF, reflux, 6 h) of 5′-*O*-benzoyl-2,3′-anhydrothymidine followed by reduction (10% Pd–C, MeOH) and formylation with acetic formic anhydride.[12] Nucleoside **26** reacted slowly with an excess of **3** to produce the isocyanide **27** as a viscous oil {$[\alpha]_D^{20}$ −18.3 (*c* 0.2, $CHCl_3$)}, in good yield, following reaction at room temperature for 36 h (entry 23).



26 X = NHCHO
27 X = NC

In summary, we have demonstrated the successful utilisation

of the Burgess Reagent in the synthesis of isocyanides from formamides and applied the reagent to a group of substrates of general interest.

Experimental

Preparation of 5

Reagent **3** (0.35 g, 1.5 mmol) was added in one portion to a solution of **4** (0.18 g, 1 mmol) in dry dichloromethane (25 ml). The solution was heated at reflux, under a nitrogen atmosphere, until TLC analysis indicated that the formamide had been consumed (80 min), then cooled, diluted with dichloromethane (20 ml), washed with water (2 × 20 ml) and dried ($MgSO_4$). Evaporation of the organic solution under vacuum and dry flash chromatography of the residue on silica gel 60, using 5% dichloromethane in hexanes as eluent, gave **5** (0.14 g, 88%) as a clear oil which darkened rapidly on standing; ν_{max}(film)/cm^{-1} 2988, 2926, 2132, 1453, 1378, 1172 and 986; δ_H($CDCl_3$, 270 MHz)‡ 1.41 (3H, d, *J* 2), 1.50 (5H, s + m), 1.61 (3H, s), 2.05 (2H, m), 5.08 (1H, t, *J* 7), 5.22 (1H, d, *J* 9.4), 5.45 (1H, d, *J* 16.4), 5.68 (1H, m); δ_C($CDCl_3$, 67.5 MHz) 17.7, 22.8, 25.5, 29.6, 41.3, 62.6, 114.0, 122.4, 132.7, 138.1, 155.7; *m*/*z* (EI) 163 (M^+), 149, 121, 91, 84, 69, 55, 49 and 41 (100%).

Acknowledgements

We thank University College Cork, Cork Corporation and Forbairt (EOLAS) for financial support to S. M. C. and H. K. C. and The Federation of Irish Chemical Industries for a bursary to H. K. C. We are grateful to Dr A. R. Maguire for helpful discussions regarding the synthesis of compound **26**.

‡ *J* Values are given in Hz.

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Paper 7/08081F
Received 10*th November* 1997
Accepted 13*th January* 1998