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NEW METHOD FOR HOFMANN REARRANGEMENT

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Summary: Treatment of a series of primary aliphatic and aromatic carboxamides (1a-1m) with NBS-$Hg(OAc)_2$-R'OH (A), dibromantin-$Hg(OAc)_2$-R'OH (B), NBS-AgOAc-R'OH (C), or dibromantin-AgOAc-R'OH (D) in DMF under argon provides corresponding carbamates (2a-2m) in nearly quantitative yields.

The Hofmann rearrangement is the conversion of primary carboxamides to amines or carbamates having one less carbon[1]; it is a useful reaction for organic synthesis, e.g., the retro-inverso peptide modification[2].

The reaction, which is an oxidative rearrangement, has been carried out by NaOBr[1a,3], CH_3OBr[4], $Pb(OAc)_4$[5], $C_6H_5I(OCOCF_3)_2$[6], C_6H_5IO[7], or $C_6H_5I(OTs)OH$[8]; however, these reagents have proved to be not practical in respect of the reaction condition and the scope.

In connection with our studies on the bromonium ion (Br^+) or its equivalent generated from N-bromosuccinimide (NBS)[9], 1,3-dibromo-5,5-dimethylhydantoin (dibromantin)[9b,c], and N-bromophthalimide[9b,c] in N,N-dimethylformamide (DMF), we attempted applying the Br^+ to new procedures for the Hofmann rearrangement. Herein we wish to report four new and practical methods for the conversion of a series of primary aliphatic and aromatic carboxamides 1 into the corresponding carbamates 2, by using NBS-$Hg(OAc)_2$-R'OH (A), dibromantin-$Hg(OAc)_2$-R'OH (B), NBS-AgOAc-R'OH (C), or dibromantin-AgOAc-R'OH (D) in DMF.

$$\underset{\underline{1}}{RCONH_2} \xrightarrow[DMF]{A\ (B,\ C,\ or\ D)} \underset{\underline{2}}{RNHCO_2R'}$$

A typical procedure is as follows: To a solution of benzamide 1h (50 mg, 0.41 mmol) and $Hg(OAc)_2$ (159 mg, 0.49 mmol) in 2 ml of DMF, MeOH (395 mg, 12.3 mmol) was added, followed by addition of a solution of NBS (96 mg, 0.54 mmol) in 1 ml of dry DMF at room temperature under argon. After the reaction mixture was stirred for 12 hours at room temperature, it was evaporated under reduced pressure to remove excess of MeOH;

diluted with 300 ml of EtOAc; washed successively with H_2O (20 mlx2), 5% HCl (20 mlx2), sat $NaHCO_3$ (20 mlx2); dried over anhyd. $MgSO_4$; and evaporated to give 68 mg of pale yellow semisolid. This was purified with silica gel column chromatography (hexane;EtOAc=3:1) to give 60 mg of colorless needles, mp 46°C (lit.[10] 47°C) (yield 96%). The reactions for the other carboxamides and methods were performed in a similar manner, and the results are summarized in Table I.

Table I. The conversion of carboxamides 1 to carbamates 2.

$RCONH_2$ 1 R	% yield of $RNHCO_2R'$[a,b] 2 A[c]	B[c]	C[c]	D[c]
a $CH_3(CH_2)_6$	91	95	93	95
b $CH_3(CH_2)_8$	100	100	95	100
c $CH_3(CH_2)_{14}$	95	100	95	94
d $CH_3(CH_2)_3CH(C_2H_5)$	96	100	91	96
e cyclohexyl	100	95	89	91
f $(CH_3)_3C$	100	100	53	75
g $C_6H_5CH_2$	95	100	93	96
h C_6H_5	96	98	91	100
i p-$NO_2C_6H_4$	92	96	90	95
j o-$EtOC_6H_4$	100	98	87	100
k o-MeC_6H_4	100	100	96	100
l o-ClC_6H_4	100	100	92	96
m 3-pyridyl	96	100	92	100

a R' are methyl groups except for 2f ($R'=CH_2C_6H_5$).

b All products gave satisfactory spectral data.

c The molar ratio of the reagents is as follows; $RCONH_2$(1.0), NBS(1.3) (or dibromantin(1.0), $Hg(OAc)_2$(1.2) (or AgOAc(1.2)), and R'OH(12.3[d]). The conversion was performed at room temperature, or at 45°C in the case of 1b, 1c, and 1i, for 12 hours[e].

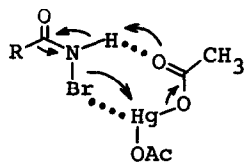
d The requisite molar ratio was not investigated closely.

e According to the carboxamides 1, the reaction time can be shortened.

Although the mechanism is not exactly known, it is conceivable that the heterolytic N-Br bond cleavage of NBS (or dibromantin) by the help of DMF[9b] starts with the formation of N-bromocarboxamide 3, which can be transformed to the isocyanate 4, the intermediate for the Hofmann rearrangement, via 5. The conversion of 4 to the carbamate 2 is a well-documented process.

$$\underline{1} + \text{NBS} \underset{}{\overset{\text{DMF}}{\rightleftharpoons}} \underset{\underline{3}}{\text{RCONHBr}} + \text{Succinimide}$$

$$\underline{3} + \text{Hg(OAc)}_2 \longrightarrow \text{RN=C=O} + \text{HgBrOAc} + \text{AcOH}$$



$\underline{5}$

As seen in Table I, all the carboxamides (1a-1m) were converted to the carbamates (2a-2m) in excellent yields under a mild neutral condition. The Hofmann rearrangement of higher aliphatic carboxamides is usually difficult[1], and aromatic carboxamides can not be converted by using $C_6H_5I(OCOCF_3)_2$[6], C_6H_5IO[7], or $C_6H_5I(OTs)OH$[8]; whereas by using our reagents the higher aliphatic amides (1a-1d) and the aromatic carboxamides (1h-1l) could be transformed to the carbamates (2a-2d and 2h-2l) in excellent yields.

In addition to the fact that NBS, dibromantin, $Hg(OAc)_2$ and AgOAc are commercially available and relatively cheap, it appears that NBS and dibromantin are not so strong oxidizing agents as those aforesaid such as $Pb(OAc)_4$ and $C_6H_5I(OCOCF_3)_2$.

As is evident from the yields given in Table I, there was no difference between NBS and dibromantin, and except for only 1f, neither was there between $Hg(OAc)_2$ and AgOAc.

Therefore our methods can be applied very practically for the Hofmann rearrangement.

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References

1. (a) E. F. Wallis and J. F. Lane, "Organic Reactions, Vol. 3", John Wiley & Sons, New York (1946), pp. 267-306 and references cited therein. (b) J. March, "Advanced Organic Chemistry", (3rd ed.), John Wiley & Sons, New York (1985), pp. 983-984 and references cited therein.

2. (a) W. D. Fuller, Murray Goodman, and M. S. Verlander, J. Am. Chem. Soc., 107, 5821 (1985). (b) M. Chorev, and M. Goodman, Int. J. Peptide Protein Res. 21, 258 (1983). (c) M. Chorev, S. A. MacDonald, and M. Goodman, J. Org. Chem., 49, 821 (1984). (d) M. Goodman and M. Chorev, Acc. Chem. Res., 12, 1 (1979). (e) M. Chorev, C. G. Wilson, and M. Goodman, J. Am. Chem. Soc., 99, 8075 (1977).
3. (a) S. Kajigaeshi, T. Nakagawa, S. Fujisaki, A. Nishida, M. Noguchi, Chem. Lett., 1984, 713. (b) S. Kajigaeshi, K. Asano, S. Fujisaki, T. Kakinami and T. Okamoto, Chem. Lett., 1989, 463.
4. (a) P. Radlick and L. R. Brown, Synthesis, 1974, 290. (b) T. Shono, Y. Matsmura, S. Yamane, and S. Kashimura, Chem. Lett., 1982, 565.
5. (a) H. E. Baumgarten, H. L. Smith, and A. Staklis, J. Org. Chem., 40, 3554 (1975). (b) B. Acott, A. L. J. Beckwith, and A. Hassanali, Aust. J. Chem., 21, 185 (1968). (d) idem, ibid., 21, 197 (1968). (e) B. Acott and A. L. J. Beckwith, Chem. Comm., 1965, 161.
6. (a) G. M. Loudon, A. S. Radhakrishna, M. R., Almond, J. K. Blodgett, and R. H. Boutin, J. Org. Chem., 49, 4272 (1984). (b) R. H. Boutin and Loudon, ibid., 49, 4277 (1984). (c) A. S. Radhakrishana, M. E. Parham, R. M. Riggs, G. M. Loudon, ibid., 44, 1747 (1979).
7. A. S. Radhakrishana, C. G. Rao, R. K. Varma, B. B. Singh, S. P. Bhatnagar, Synthesis, 1983, 538.
8. I. M. Lazbin and G. H. Koser, J. Org. Chem., 51, 2669 (1986).
9. (a) P. A. Bartlett, "Asymmetric Synthesis, Vol.3, Part B", ed. by J. D. Morrison, Academic Press, New York (1984), Chap. 2, pp. 421-423 and references cited therein. (b) Chae-ho Cook, Youn-sang Cho, Sang-sup Jew, Young-guh Suh and Eung-ku Kang, Arch. Pharm. Res., 6, 45 (1983). (c) Chae-ho Cook, Youn-sang Cho, Sang-sup Jew, and You-sup Chung, Seoul Uni. J. Pharm. Sci., 9, 44 (1984).
10. A. I. Kizber and A. S. Glagoleva, Zh. Obschch. Khim., 23, 1028 (1953); Chem. Abstr., 48, 8790 (1954).

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