

Microwave-Mediated Pyrazole Fluorinations Using Selectfluor[®]

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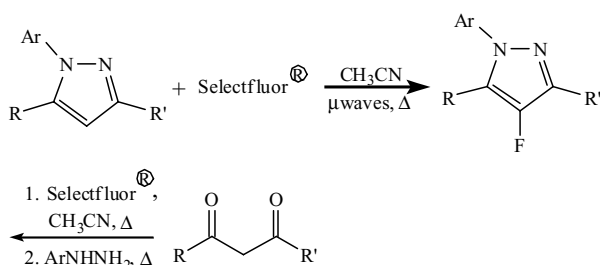
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ABSTRACT: Microwave-mediated electrophilic fluorinations and a new single-pot condensation en route to ring-fluorinated pyrazoles were examined:



The monofluorination by these methods was successful for a variety of pyrazoles, with yields ranging from 13% to 75%. While electrophilic aromatic fluorination of 3-CF₃ pyrazoles proved largely ineffective, development of a single-pot process overcame this limitation. The microwave-mediated reaction is regioselective; ring fluorination of the heterocycle occurs preferentially over phenyl and alkyl substituents. Alkyl side chain fluorination, when desired, can be modulated by reactant ratios. The single-pot method, which involves acid catalysis by H-TEDA, produces

4-fluoropyrazoles products. © 2009 Wiley Periodicals, Inc. Heteroatom Chem 20:341–345, 2009; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20556

INTRODUCTION

The preparation of fluorinated pyrazoles, important precursors to pharmaceuticals and pesticides [1–4], has been the subject of extensive investigation. The usual means of introducing fluorine selectively into aromatic systems have included fluorinated synthons, the Balz–Schiemann process, dilute fluorine gas mixtures, or nucleophilic aromatic substitution with fluoride anion [5–13]. In many cases, multiple steps are required; special glassware is necessary, and yields are not optimal.

Over the past decade, expansion of uses for the F-TEDA family of electrophilic fluorinating reagents such as Accufluor[®] and Selectfluor[®] has been dramatic. Reaction conditions vary widely, with many processes requiring refluxing conditions to achieve good yields. While examples of these reagents' utility in electrophilic heteroaromatic fluorinations of selected heterocycles such as isoxazoles, pyridines, and thiazoles are known, the studies concerning pyrazoles conducted thus far have remained limited in scope and discussion of substrate reactivity [14–16]. Furthermore, electrophilic fluorination of alkyl side chains on heteroaromatic systems with Selectfluor[®] has not been reported in the literature.

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Our efforts were directed toward accomplishing several objectives. First, preparation of a variety of ring-fluorinated pyrazoles substituted with electron-withdrawing groups (EWGs) and electron-donating substituents (EDGs) would provide a more complete picture of Selectfluor®'s effectiveness as an electrophilic pyrazole fluorinating agent. In addition to the reactivity study, a selectivity investigation of the tendency of Selectfluor® to fluorinate aryl and alkyl functional groups on pyrazolic species will be reported. Finally, we will take advantage of the susceptibility of 1,3-diketones to fluorination in the 2-position by F-TEDA reagents [17] and to examine the ability of H-TEDA to act as an acid catalyst in the condensation of in situ generated 2-fluoro-1,3-diketones with arylhydrazines in a novel one-pot route to new pyrazole species.

RESULTS AND DISCUSSION

Scheme 1 shows the pyrazoles prepared in this work by electrophilic aromatic fluorination (method A). Diketones **1a**, **c–e** are available commercially; **1b** and **1f** were prepared by literature methods [18].

Fluorinations of pyrazoles via the method A, unless otherwise noted, were carried out using 6×5 min heating cycles in a standard 1450-W microwave oven operating at a 10% power level. Microwave-mediated conditions were chosen for the more than 50-fold reaction time savings when compared to conventional reflux methods. In addition, a side-by-side comparison of fluorinations of **2a** using the microwave-mediated process (0.5 h) and standard reflux conditions (24 h) showed that the microwave technique afforded a higher product yield: 60% versus 53%.

Pyrazole regioisomers **2b–d**, **4c**, **8e**, and **8f** were identified by NMR chemical shifts of the pyrazolic ring proton H_1 ($\delta = 6.7$ – 6.9 ppm) and by ^{19}F NMR where $\text{R}' = \text{CF}_3$ ($\delta(\text{CF}_3) \approx -62$ ppm). Ring-fluorinated pyrazole regioisomers **3a–d**, **5a**, **5c**, **7a**, **9a**, **9e**, and **9f** were identified and assigned by ^{19}F NMR chemical shifts of the pyrazolic ring fluorine ($\delta(\text{F}) \approx -171$ to -176 ppm) and where $\text{R}' = \text{CF}_3$ ($\delta(\text{CF}_3) \approx -62$ ppm).

General trends are evident from Scheme 1. In agreement with previous findings, alkyl-substituted 1,3-diketones gave higher yields of *N*-arylpyrazoles than aryl-substituted 1,3-diketones [6]. Arylhydrazines substituted with EDGs gave higher yields of pyrazoles than those substituted with EWGs. The diketone-hydrazine condensation in the method A led predominantly to the 3- CH_3 or 3- CF_3 pyrazole in all cases except pyrazoles **2c** and **8f**, for which both the 3- CF_3 and 5- CF_3 pyrazole regioisomers were

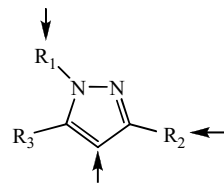


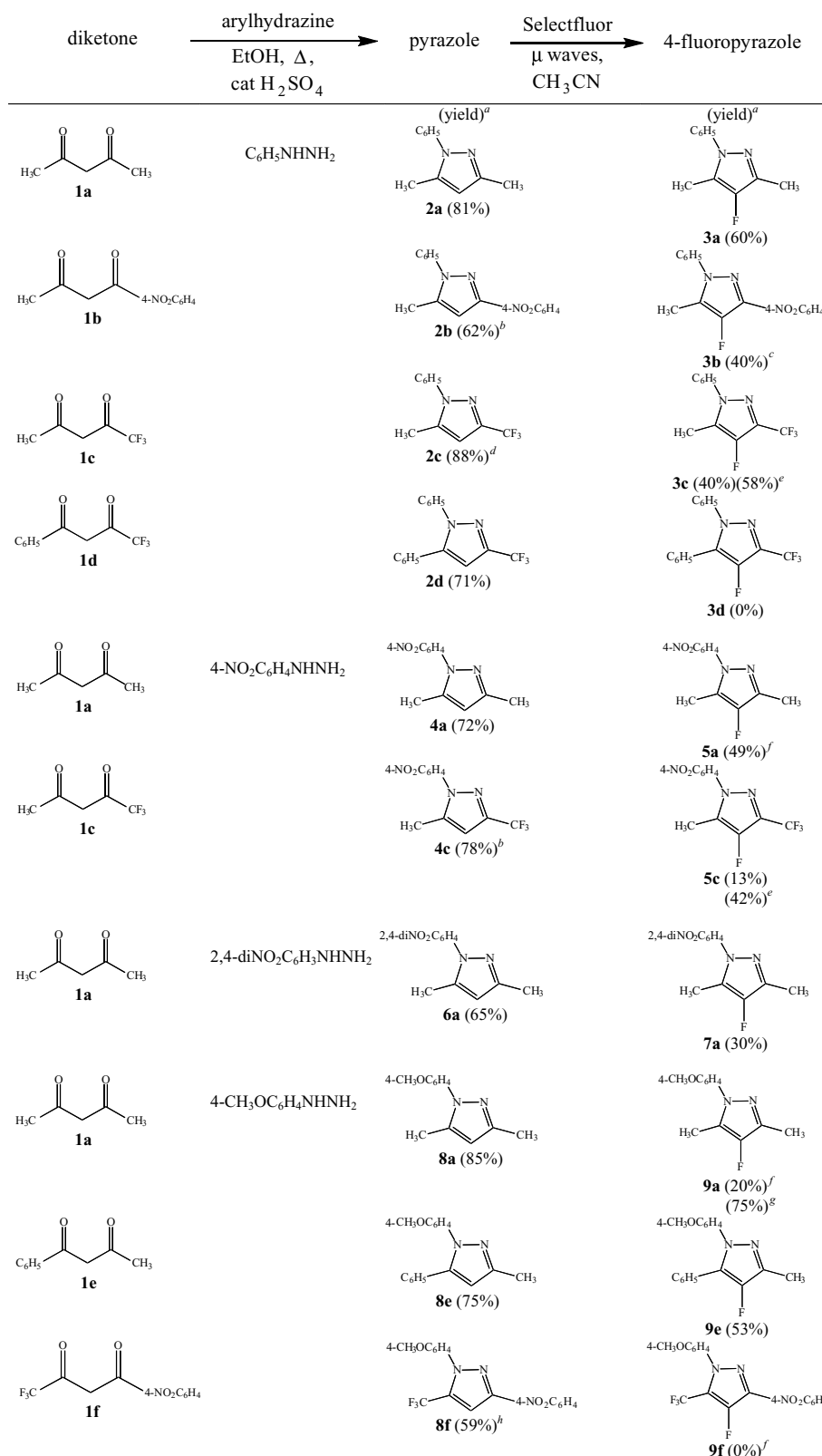
FIGURE 1 Fluorination sites observed.

obtained in 1:1 and 2:1 ratios, respectively. This preference, in accord with previous work, is likely due to a combination of steric and stereoelectronic effects in the initial nucleophilic addition of the arylhydrazine to the diketone [5,6].

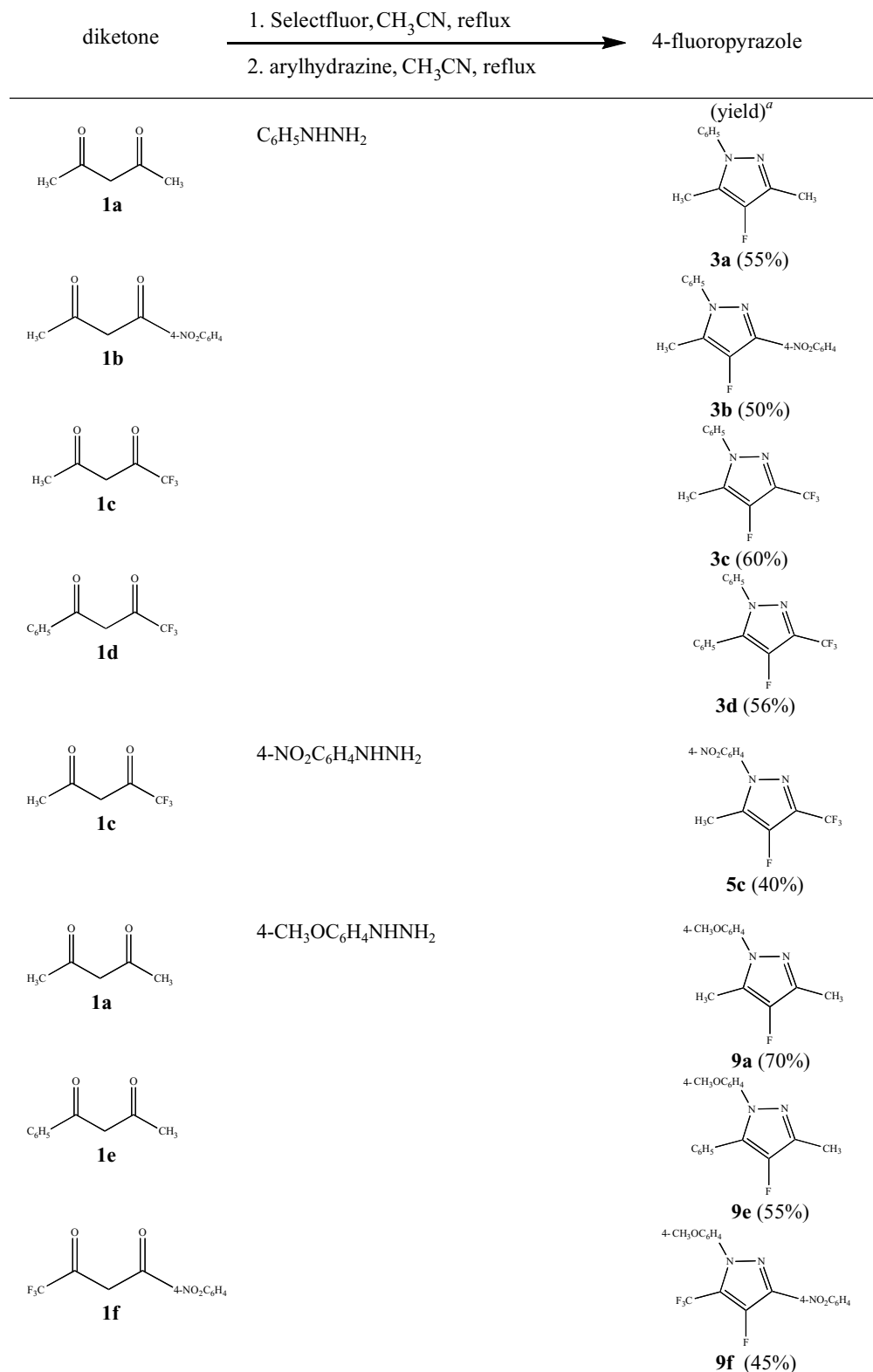
As expected, reactivity of the pyrazole system toward electrophilic aromatic fluorination was modulated by substituents. Deactivated pyrazoles, e.g., compounds **2b–2d**, **4a**, **6a**, and **8f**, generally gave lower yields of the ring-fluorinated pyrazoles, whereas activated pyrazoles (**2a**, **8a**, and **8e**) led to improved yields.

Likewise, substituents affected fluorination regioselectivity. Figure 1 shows the sites of fluorination observed. In nearly all cases, the ring-fluorinated pyrazole was the major product. Fluorination of R_1 ($\text{R}_1 = 4\text{-CH}_3\text{OPh}$) was observed by ^{19}F NMR in pyrazoles **8a**, **8e–f**. Attempts to fluorinate the activated pyrazole **8a** under microwave-mediated conditions led to a complex mixture of mono- and difluorinated products after only 2×5 min heating cycles. Consequently, pyrazole **9a** was prepared in 75% yield under very mild reaction conditions (room temperature, 24 h). R_1 -fluorinated pyrazole derivatives of compounds **8e** and **8f** accounted for approximately 5% and 10% of the product mixtures, respectively. Two additional products were verified by ^{19}F NMR (δ , CFCl_3): fluorination of the anisyl ring at C-3: s, 1F, -110 ppm; at C-2: s, 1F, -108 ppm. Two examples of fluorination at R_2 occurred: ($\text{R}_1 = 4\text{-NO}_2\text{Ph}$, $\text{R}_2 = \text{CH}_3$) 4-fluoro-3-fluoromethyl-5-methyl-1-(4-nitrophenyl)pyrazole (**5b**) was isolated in 20% yield, and ($\text{R}_1 = 2,4\text{-NO}_2\text{Ph}$, $\text{R}_2 = \text{CH}_3$) 4-fluoro-3-fluoromethyl-5-methyl-1-(2,4-dinitrophenyl)pyrazole was identified by ^1H and ^{19}F NMR (10%) but not isolated. It is also of interest that fluorination at R_3 ($\text{R}_3 = \text{Ph}$, CH_3) was not observed; this is undoubtedly a consequence of steric interference between R_3 and F-TEDA. To verify this preference, pyrazoles **2a** and **4a** were subjected to fluorination with 4 equiv of Selectfluor® and pyrazoles **3c** and **5c** were isolated in 58% and 42% yields, respectively.

Ring-fluorinated pyrazoles produced by the method B were obtained via in situ fluorination of



SCHEME 1 Microwave-mediated pyrazole synthesis. ^aYield after purification. ^bRegioisomeric pyrazole formed in 10% yield. ^cPyrazole **3b** formed exclusively. ^dRegioisomeric pyrazole also produced in 1:1 ratio. ^eYield: **3c** from **2a** and 4 eq Selectfluor®; **5c** from **4a** and 4 equiv Selectfluor®. ^fMultiple fluorinated products produced. ^gYield under modified conditions. ^hRegioisomeric pyrazole also produced in 1:2 ratio.

SCHEME 2 One-pot fluorinated pyrazole synthesis. ^aYield after purification.

the diketones (acetonitrile, 70°C, 24 h). The monofluorinated diketones of **1a**, **1c**, and **1d** were isolated and identified by ^{19}F NMR to verify the reaction pathway. The in situ generated diketones then underwent H-TEDA catalyzed condensation with the arylhydrazines (acetonitrile, 70°C, 24–40 h) to provide the 4-fluoropyrazoles are shown in Scheme 2.

The method B led to formation of the 3- CH_3 , 4-F- and 3- CF_3 , 4-F-pyrazole isomers, with the singular exception **3b**, which gave the 3-(4- NO_2Ph), 4-F-pyrazole. The trifluoromethyl group regioselectivity observed in the single-pot process is accounted for by the preference for the keto form of the in situ generated 2-fluoro-1,3-diketone formed prior to condensation with arylhydrazines to the pyrazole [5]. Nucleophilic addition by the arylhydrazines occurred at the most electrophilic site, e.g., the carbonyl adjacent to the $-\text{CF}_3$ or 4- NO_2Ph group. This strategy eliminated the likelihood of side reactions; no fluorination of alkyl or aryl groups was observed.

CONCLUSION

This study of pyrazole formation provides new insight regarding the effectiveness and selectivity of the F-TEDA class of reagents in electrophilic aromatic fluorinations and how reaction conditions may be modified to improve yields and regioselectivity. In addition, the effect that substituents have on influencing product regioselectivity and reactivity for this important condensation involving arylhydrazines and 1,3-diketones has been outlined.

This work shows that Selectfluor[®] is an effective electrophilic-fluorinating agent for pyrazoles, which are not highly deactivated. Yields are commensurate with those of other multiple-step processes, and reaction times are dramatically reduced. Overall, monofluorinated pyrazoles are the major product unless an activated benzene ring is present. Exceptions noted appear to be influenced by a combination of steric and stereoelectronic effects.

We have also demonstrated that Selectfluor[®] provides not only selective fluorination capability, but its ammonium salt byproduct of that fluorination also catalyzes 4-fluoropyrazole formation in comparable yields to previous methods. This novel, single-pot approach is effective irrespective of substituents on the 1,3-diketone or arylhydrazine. This process offers a new route for selective incorporation of fluorine into pyrazolic molecules that is without the use of toxic or unstable fluorinating agents, specialized reaction conditions, or isolation of intermediates.

SUPPORTING INFORMATION

Experimental details are available from the corresponding author on request [5,6,18–24].

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REFERENCES

- [1] Genin, M. J.; Biles, C.; Keiser, B. J.; Poppe, S. M.; Swaney, S. M.; Tarpley, W. G.; Yagi, Y.; Romero, D. L. *J Med Chem* 2000, 43, 1034.
- [2] Guzman-Perez, A.; Wester, R. T.; Allen, M. C.; Brown, J. A.; Buchholz, A. R.; Cook, E. R.; Day, W. W.; Hamanaka, E. S.; Kennedy, S. P.; Knight, D. R.; Kowalczyk, P. J.; Marala, R. B.; Mularski, C. J.; Novomisle, W. A.; Ruggeri, R. B.; Tracey, W. R.; Hill, R. J. *Bioorg Med Chem Lett* 2001, 11(6), 803.
- [3] Penning, T. D.; Talley, J. J.; Bertenshaw, S. R.; Carter, J. S.; Collins, P. W.; Docter, S.; Graneto, M. J.; Lee, L. F.; Malecha, J. W.; Miyashiro, J. M.; Rogers, R. S.; Rogier, D. J.; Yu, S. S.; Anderson, G. D.; Burton, E. G.; Cogburn, J. N.; Gregory, S. A.; Koboldt, C. M.; Perkins, W. E.; Seibert, K.; Veenhuizen, A. W.; Zhang, Y. Y.; Isakson, P. C. *J Med Chem* 1997, 40, 1347.
- [4] Suschitzky, H. *Adv Fluorine Chem* 1965, 4, 1.
- [5] Bumgardner, C.; Sloop, J. *J Fluorine Chem* 1992, 56, 141.
- [6] Sloop, J.; Bumgardner, C.; Loehle, W. *J Fluorine Chem* 2002, 118, 135.
- [7] Ishikawa, N. *Bull Chem Soc Japan* 1981, 59, 3221.
- [8] Linderman, R.; Kirolos, K. *Tetrahedron Lett* 1989, 30(16), 2049.
- [9] Norris, T.; Colon-Cruz, R.; Ripin, D. H. B. *Org Biomol Chem* 2005, 3, 1844.
- [10] Singh, S.; Kumar, D.; Batra, H.; Naithani, R.; Rozas, I.; Elguero, J. *Can J Chem* 2000, 78, 1109.
- [11] Doyle, M. P.; Bryker, W. J. *J Org Chem* 1979, 44, 1572.
- [12] Katoch-Rouse, R.; Hortu, A. G. *J Labelled Compd Radiopharm* 2003, 46(1), 93.
- [13] Ichikawa, J.; Kobayashi, M.; Noda, Y.; Yokota, N.; Amano, K.; Minami, T. *J Org Chem* 1996, 61(8), 2763.
- [14] Stephens, C. E.; Blake, J. A. *J Fluorine Chem* 2004, 125(12), 1939.
- [15] Pace, A.; Buscemi, S.; Vivona, N. *Org Prep Proc Int* 2007, 39, 1.
- [16] Lal, G. S.; Pez, G. P.; Syvret, R. G. *Chem Rev* 1996, 96, 1737.
- [17] Xiao, J.; Shreeve, J. M. *J Fluorine Chem* 2004, 126(4), 473.
- [18] Reid, J.; Calvin, M. *J Am Chem Soc* 1950, 72, 2948.
- [19] Haddadin, M. J. *Tetrahedron* 1976, 32(6), 719.
- [20] Dilli, S.; Robards, K. J. *Chromatogr* 1984, 312, 109.
- [21] Ried, W.; Muehle, G. *Justus Liebigs Ann Chem* 1962, 656, 119.
- [22] Paul, R.; Tchelitcheff, S. *Bull Chim Fr* 1958, 11, 4179.
- [23] Brady, O. L. *J Chem Soc* 1931, 756.
- [24] Butler, R. N.; Hanniffy, J. N.; Stephens, J. C.; Burke, L. A. *J Org Chem* 2008, 73(4), 1354.